BASEDOW'S DISEASE

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The Manifestations, Timing, Duration and Outcome of Basedow's Disease; Symptoms, Severity and Age Incidence; the Disease in Children; and Its Occurrence Among Animals

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Foreword

Some eight years ago, in the process of searching the medical literature to determine the influence of various forms of treatment on the course of hyperthyroidism, it became apparent that full records of earlier observations were hard to find in medical reference libraries. More recent publications described the effectiveness of thyroidectomy, iodine, and other measures; few described the disease itself and the outcome when no specific treatment was applied. Then, from his personal library, Dr. J. H. Means kindly provided a copy of Sattler's *Die Basedowische Krankheit*. This exhaustive review obviously contained all the information likely to be found on the subject previous to 1907. When inquiries among dealers in old medical books elicited that it was out of print and that not even a used copy of this valuable contribution to medical science was to be had, it seemed time for publication of an English translation.

Mrs. G. W. Marchand, wife of the late German biologist, agreed to undertake the burden of translating the work. Thoroughly familiar with both languages and with science, she was ideally equipped for the enormous task. With the help of her son, Dr. John F. Marchand, she completed the project in seven years while continuing her professional duties in education. Doctor Marchand, though busily engaged in medical practice, revised the entire manuscript to simplify the ponderous German phraseology and insure accuracy of medical terminology. The product of these arduous labors is a faithful translation, paraphrased to clarify the meaning but not so extensively as to lose all flavor of the original. The extensive bibliography of 3210 references was reproduced without alteration.

In view of the great expense involved in publishing a treatise of this length, many difficulties presented themselves. These were surmounted only through the foresight and experience of Mr. Henry M. Stratton. With full realization that it could not be a commercial venture, Grune and Stratton offered to publish the translation and to underwrite part of the mechanical costs as a contribution to clinical medicine and endocrinology.

Sustaining support for the project was provided by a generous grant from the Lederle Laboratories Division of the American Cyanamid Company, Pearl River, New York. Without this financial aid it would not have been possible to reproduce the work except for distribution at a premium; with it, this nicely wrought volume is presented at a nominal price.

Those of us who will use the book as a source of reference, and those who will read it for its wealth of practical material on a fascinating subject, will remain continually grateful to the Marchands, Doctor Means, Mr. Stratton, and to Lederle, for placing the volume at our disposal.

Boston
September 1952

E. B. Astwood

Hubert Sattler*

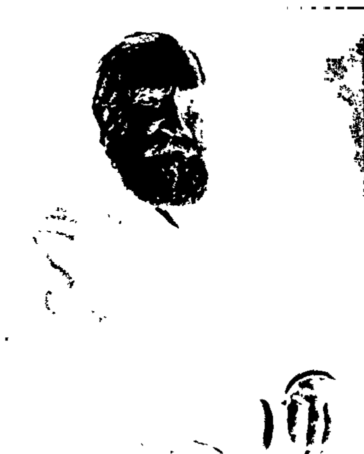
THE SCIENCE OF OPHTHALMOLOGY and our Archive suffered a heavy loss on November 15th in the death of Hubert Sattler, Dean of German ophthalmologists. He had reached the age of eighty-five. Sattler belonged to a generation whose growing knowledge of diseases of the eye had attracted von Graefe, Helmholtz, Donders and Arlt to this field

Sattler was born in Salzburg on September 9, 1844. In 1872, at the age of 28, he joined the staff of Arlt's clinic in Vienna. From this illustrious master of the Vienna school he acquired a high degree of technical skill and a lasting interest in the task of ophthalmology on a more scientific basis By several investigations, particularly on bacteriological aspects, he contributed significantly to the development of modern ophthalmology In the first edition of the *Graefe-Samisch Handbuch* he wrote the excellent section on "Pulsating Exophthalmia and Basedow's Disease." In the second edition of this *Handbuch* he presented a comprehensive discussion of the entire subject of Basedow's Disease At the age of 80 he completed a monograph, published in 1925, on "Malignant Tumors of the Eye" He taught at the Universities of Giessen, Erlangen, Prague From 1891 to 1920 he had an unusually capable series of students at Leipzig. Many of them now teach in our universities

Sattler was a distinguished physician and a master of operative technique He treated a long series of patients with unfailing and generous devotion His love of nature, especially the mountains, and a sensitive appreciation of music and art enriched a life which had been extraordinarily active and productive

Following the death of his former teacher, Arlt, Sattler took his place in 1888 as one of the editors of this Archive. He entrusted to it the publication of much of his own valuable work as well as numerous articles by his students The Ophthalmological Society has lost an old and devoted member, one who attended meetings with the greatest regularity, and who often contributed important and stimulating reports of his investigations He was always actively interested in our Society, and served on its Advisory Board for 37 years, from 1881 to 1918. As the years pass, one may reflect in gratitude on what he accomplished toward the advancement of ophthalmology. May his name be long remembered

* A. Wagenmann Obituary von Graefe's *Archiv für Ophthalmologie, 121*, Part 2, p I-II, 1929



Hofphotograph E. Hoenisch, Leipzig

Dr H. Sattler.

Preface

SINCE MY ACCOUNT of Basedow's disease in the first edition of this handbook in the year 1880, clinical observations have become so extensive, and scientific viewpoints altered so much that a complete revision and a considerable enlargement have become necessary

Naturally I have devoted the most detailed study to those symptoms which concern the eyes and the region around them. But it has seemed to me indispensable to devote to the other signs a discussion adequate to our present knowledge, since a proper evaluation of the former would be hard to attain without a complete understanding of the latter Also I believe that it may not be unwelcome to the doctor of internal medicine, the neurologist, and also to the surgeon to have on hand a detailed description and a critical treatment of Basedow's disease from the standpoint of the ophthalmologist, since not a few more or less important signs manifest themselves on the eyes and eye-lids and in their paths and centers of innervation Finally it must also be remembered that since the publication of the second not very extensively revised edition of Mobius's well-known discussion of Basedow's disease in the Handbook of Special Pathology by Nothnagel, in which the symptomatology was treated only too briefly in parts, no other detailed description has appeared.

In the bibliography, which is brought up to the year 1907, I have tried to fill the many gaps which appear in the bibliographies in the monographs of Buschan (1894) and Mobius (1896) and to correct the many erroneous references of the former as well as to avoid such errors myself.

Part I covers the symptomatology Part II comprises the important sections on the various forms of the disease, on progress and outcome, relation to age and sex, geographical distribution, Basedow's disease in animals, influence of heredity, etiology, pathological anatomy, history and pathogenesis, diagnosis, prognosis, and therapy

H SATTLER

Leipzig
December 1908

Translators' Preface

Hubert Sattler's direct observations and his literature search covering the years 1722 to 1909 provide a reference work of first magnitude on the natural course of diseases of the thyroid. Sattler has contributed a general treatment of the subject encompassing world literature antedating general use of methods of treatment which, since that time, have profoundly influenced the course of nearly all recognized cases. No comparable survey of relatively untreated case material has previously been available in English. As an opthhalmologist, the author was a leading spirit in the Golden Age of German medicine, one who ventured an encyclopedic approach to the ramifications of his specialty throughout the whole field of medicine, and thyroid disease in particular. The discussion of 103 cases of Basedow's disease which came under his own care, and of a total of 3800 in the literature, 3210 females and 590 males, is far more thorough and informative than any mere statistical breakdown. His interest probed and pondered the evidence on all the possible biologic, diagnostic, and therapeutic aspects of thyroid disease.

"Die Basedowische Krankheit" was compiled when metabolism testing was still at the research project stage in the Berlin physiology laboratory of Magnus-Levy. The clinical diagnosis of thyroid dysfunction was still regularly established by the signs and symptoms, rather than by a technician's report. Sattler drew on every obscure note or doctorate thesis, as well as more obvious sources. The references also include an extraordinary galaxy of pioneer clinicians, Trousseau, Romberg, Henoch, Charcot, Chvostek, Meigs, Flint, Traube, Duroziez, Hutchinson, Förster, DaCosta, and Pierre Marie, for example, authors still familiar for other work, or for the signs or syndromes which bear their names

Sattler actually undertook to evaluate each published report in terms of all the others The extent of his success with this gargantuan task is reflected in the frequency with which he has anticipated problems of present day interest, for example the relationship of thyrotoxicosis to carbohydrate metabolism, the relationship of the thyroid to cardiac function and myasthenia, the nature and meaning of the orbital or pretibial edema which sometimes accompanies thyroid disease, the frequency with which non-toxic goiters become toxic and vice versa, the significance of the psychic disorders which may lead to or accompany thyrotoxicosis, and, remarkable as it may seem, even a few accounts of the occurrence of Basedow's disease in domestic animals It seems unlikely that such a body of well studied case material on the natural history of thyroid disease could again be assembled on this scale.

G W Marchand
J F. Marchand

September 1952

Basedow's Disease, Morbus Basedowii

SYNONYMS

Glotzaugenkachexia (v Basedow)
Cachexie or dyscrasie exophthalmique or exophthalmic cachectique
Bupthalmus hystericus (Bruk)
Exophthalmus anaemicus (Prael)
Anemic exophthalmos (W. Mackenzie)
Anemic protrusion of the eyeballs (Taylor)
Struma exophthalmica
Exophthalmic goiter (exophthalmic bronchocele, Laycock)
Goitre exophthalmique
Gozzo esoftalmico, bocio exoftalmico
Graves' disease Maladie de Graves Morbus Gravesii (Mannheim)
Malattia or morbo di Flajani (Bacelli and others)
Cardiogmus strumosus (Hirsch)
Tachycardia strumosa exophthalmica (Lebert)
Nevrose thyro-exophthalmique (Corlieu)
Ataxie cardiovasculaire (Féréol)
Cachexie thyroidienne (Gauthier)

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Part II. The Forms of the Disease; Its Course, Incidence, Distribution; Basedow's Disease in Childhood

Part I. Symptomatology

Introduction

§1. BASEDOW'S DISEASE is a peculiar disease characterized by a complex of more or less *numerous signs and symptoms. The most essential and most* characteristic are classified as follows:

1. Rise in pulse rate and heart beat and a more powerful pulsation of the arteries on the neck.
2. Enlargement of the thyroid gland.
3. *Exophthalmus on both sides.*
4. A peculiar tremor.

These manifestations must be considered the cardinal signs not because they appear with regularity or because all of them are essential for a diagnosis but because, as a whole and in combination, they form a peculiar pat*tern not found in any other disease*

To these cardinal signs are added a long series of disorders, partly local, which occur in large or small numbers A few of these must be counted among the most frequent and the most significant manifestations of the disease.

Signs Involving the Heart and Larger Blood Vessels

§2. The most constant sign and, in the typical forms of the disease, the first to appear, is *tachycardia* The accelerated pulse rate is lasting By means of repeated tests it has been found that even during complete muscular relaxation the pulse rate is abnormally high In a minority of the cases it is below 100 beats per minute, usually it is between 100 and 150 beats per minute but the rate may reach or exceed 200 Mild mental excitement and slight physical *exertions increase the pulse rate considerably* Even during sleep the pulse is, as a rule, rather rapid, although only slightly so when the subject is awake During the course of the disease a wide variation in the pulse rate is frequently observed

In 178 cases of Basedow's disease in which G R Murray (2553) recorded the pulse rate, it ranged between 90 and 100 in 4 instances, between 100 and 110 in 12, between 110 and 120 in 12; between 120 and 130 in 35, between 130 and 140 in 10, between 140 and 150 in 47, between 150 and 160 in 17, between 170 and 180 in 5, between 180 and 190 in 7, and around 200 in 6 cases In 101 cases, that is, in over 50%, the pulse rate reached 120 to 150 beats per minute and in 47, that is, more than 25% it was between 140 and 150 The highest rate was found during attacks of palpitation Among my own 95 cases, 7 had a pulse rate of between 80 and 90, 11 between 90 and 100, 17 be-

Part I. Symptomatology

Introduction

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In 178 cases of Basedow's disease in which G. R. Murray (2553) recorded the pulse rate, it ranged between 90 and 100 in 4 instances, between 100 and 110 in 12, between 110 and 120 in 12, between 120 and 130 in 35; between 130 and 140 in 19, between 140 and 150 in 47, between 150 and 160 in 17, between 170 and 180 in 5, between 180 and 190 in 7, and around 200 in 6 cases. In 101 cases, that is, in over 50%, the pulse rate reached 120 to 150 beats per minute and in 47, that is, more than 25% it was between 140 and 150. The highest rate was found during attacks of palpitation. Among my own 95 cases, 7 had a pulse rate of between 80 and 90; 11 between 90 and 100; 17 be-

tween 100 and 110, 22 between 110 and 120, 19 between 120 and 130, 5 between 130 and 140, 13 between 140 and 150, and 1 had a pulse rate of 168 Thus in 39 cases it varied between 100 and 120 beats per minute and in 37 between 120 and 150.

R v Hosslin (1450) observed in 2 cases a constant dependence of the pulse rate on the time of day *The count was always higher in the morning than in the evening* and the more so the higher the latter rose (for instance, morning pulse 160, evening pulse 130, morning pulse 105, evening pulse 95 etc) Kocher (2197) made similar observations on several of his patients Kroug (2700) found in a 19 year old man with the typical Basedow symptoms quite an unusual change in the pulse rate each time the patient either stood up or lay down When he was in a recumbent position the pulse rate declined at once from 120 to about 60, following a short pause in the heart beat, a manifestation which Kroug had an opportunity to check in the patient several times later on Ohlemann, who himself suffered from Basedow's disease (reported in writing) stated that in his own case the pulse rate was higher when lying than when sitting

§3. The intensity of the heart beat usually is increased considerably; the apex beat is often more or less spread out and the action can be felt and seen distinctly not only in the region of the cardiac apex but sometimes over the whole wall of the chest as well as on the epigastrium In exceptional cases the heart beat can even be heard at a distance

Such a case has already been reported by Graves (18). "I could distinctly hear the beating when my ear was four feet away from her chest" Baumler (203, p 508) told of a similar observation Murray (2553), in one of his 180 cases, could hear distinctly, with the unaided ear, the first heart sound at a distance of one yard, that is, at about 90 cm from the chest, and in another case at a distance of several inches.

In a case reported by Coolidge (1833) an especially conspicuous symptom was a strong pulsation on the epigastrium which had begun at the outbreak of the disease with a sudden violent pain in this region Kocher (2197) observed epigastric pulsation in 5 among 80 cases Hirschl (2192) among 14 cases of Basedow's disease observed the same signs in one case which developed very rapidly

On the Roentgen screen *it can be shown that the heart* of a patient suffering from the disease presents a perfect type of *Aktion* pulse (v Cyon) (Fr. Kraus 2942)

§4. The increased strength of the heart beat usually is accompanied by a subjective feeling of *cardiac palpitation*. In many cases it is very distressing and causes oppression and a state of anxiety Not infrequently it is the cardiac palpitation itself which causes the patient to visit the doctor. However, there are cases in which there is little or no complaint of heart palpitation, especially when it has developed and increased very gradually (Wh. Cooper 31, 2nd case, Taylor 59; Fr. Chvostek 269, 11th and 15th observations, in a 46 year old man with a severe form of the disease, and many others) Simple tachycardia sometimes does not enter the consciousness of the patient at all.

A 19 year old girl under my observation, with severe Basedow's disease and strong carotid pulsation, did not complain of palpitation even after climbing stairs, although she had a pulse rate of 125 to 150 beats per minute Similar observations were made by Rendu (565), Charcot (815), Hector Mackenzie (918) and Lannois (1600).

§5. The cardiac palpitation like the acceleration of the pulse is characterized by considerable fluctuation. Even the slightest physical exertion, such as rising from a chair or walking slowly as well as the most insignificant mental upset are sufficient to increase it conspicuously. Greater exertions, however, and especially intense mental excitement often result in violent paroxysms. These may occur sometimes even without evident cause and quite suddenly while the patient is lying in bed, and they are then usually combined with a simultaneous intensification of other disease symptoms The patients not infrequently suffer from feelings of anxiety or even, in rare cases, from anginal pains or even from *angina pectoris* Sometimes the attack ends with a feeling of great exhaustion. Although they cannot properly be called attacks, the tachycardia and cardiac palpitation increase during some stages of the illness.

In many cases the cardiac palpitation as well as the tachycardia is greater in the morning (see §2 above) Sometimes it increases markedly when the patient lies down and quiets down only very gradually Sometimes the patients are waked in the night by violent palpitation Often it is more distressing when lying on the left side and more endurable when lying on the right (Ditisheim 1293, Mattiesen 1471, Kocher 2197) Michalski (2716), on the other hand, tells of a 51 year old Basedow patient in whom all the symptoms were stronger when lying on her right side at night Once the pulse rate rose from 124 to 144 within two hours while she lay on her right side, without any kind of excitement.

In a 22 year old girl observed by Ballet the cardiac palpitation increased toward the middle of the day without any cause In the severe case of a 49 year old woman Hingston Fox 969 had a pulse chart made covering a period of eight months This chart showed attacks of greatly accelerated and irregular heart action of about 24 hours duration, with intervals of from several days to a week

In a 41 year old woman, severly ill, reported by Souques and Marinesco (1660), daily paroxysms of tachycardia and palpitation of half hourly duration occurred, sometimes accompanied by symptoms of angina pectoris

Trousseau, in a study of Basedow's disease, has already mentioned the occurrence of such attacks with angina pectoris lasting several hours with painful radiations into the right shoulder P Marie (555) observed attacks in a 21 year old man, all began with a rise in the pulse and palpitation With this was combined a feeling of constriction around the heart "as if the heart were being torn out", a fear of death,

and a pain in the left shoulder The attacks always ended with an imperative need to urinate and an abundant discharge of urine Once or twice there was a loss of consciousness for a short time Concerning attacks of angina pectoris in Basedow's disease, reports have been made by Habershon (310) in a very severe case, by Ormby (731), Aubry (801), and Perregaux (1233) The last two reported male patients in whom the disease was complicated by pronounced hysterical symptoms In a 23 year old patient of Koeppen's (1051) symptoms of *angina pectoris* appeared shortly before death. A 37 year old patient with Basedow's disease whose history is reported by Roper (1911) two days before his death underwent severe attacks of angina pectoris preceded a week earlier by an attack of precordial anxiety Ingelrans (1741) told about a 45 year old woman who suffered for years from attacks of tachycardia with strong carotid pulsations, flushing of the face, severe palpitation and angina pectoris as well as a pain radiating from the region of the heart Most of these reports do not make it clear whether, in these cases, sclerosis of the coronary arteries existed Roper's description states "left side of heart eccentrically extended, valves unaltered, left coronary artery conspicuously small, its cross-section scarcely 1 mm "

A 38 year old patient of Jacobsohn (1739) often had a frightening sensation in the heart region, concurrently with heavy cardiac palpitation and a very rapid pulse, up to 160 beats per minute or more Furthermore a noticeable goiter appeared at this time Trembling of the hands increased A 22 year old patient of Mosslein's (1450) had severe attacks of tachycardia These lasted several hours, or even weeks, during which the pulse rate rose quite suddenly from 130 to 200 or even 250 beats per minute Then, just as suddenly as the attack had started, recovery took place, the patient experiencing a jerk in the form of a very violent cardiac contraction and a feeling of extreme exhaustion of about an hour's duration Angel Money (674) described such attacks, of about 20 minutes duration, in a 36 year old woman, during which the pulse exceeded 200 beats per minute accompanied by a voluminous outbreak of facial perspiration C Gerhardt (1105) observed a case in which, at the slightest cause, or often with no ostensible cause, attacks of tachycardia and palpitation occurred with throbbing in the temples, redness and warmth of the face, increased tremor and frequent stools The pulse rose at the same time to 200 beats per minute and became almost indistinguishable as well as frequently irregular

Among Kocher's (2197) various and instructive 80 cases the feeling of intermittent attacks of cardiac palpitation occurred in 5, while a corresponding rise in pulse would not be determined objectively In a 32 year old man, however, the tachycardia and palpitations increased at intervals During these attacks a systolic thrust of the cardiac apex was evident which was absent at other times The eyes protruded somewhat, whereas no exophthalmia was present during the intervals In a 32 year old woman the pulse which otherwise had a rate of 80 to 90 beats per minute rose *during* the attacks, accompanied by exacerbation of the other symptoms in the *form* of severe tremors and became almost impossible to count

Kobisch (2303) tells about a 23 year old woman with Basedow's disease in whom several sudden paroxysms of tachycardia occurred with a pulse rate of 180 to over 200 beats per minute accompanied by pain in the region of the heart, nausea, sleeplessness and polyuria

One of our patients, a 28 year old woman with typical Basedow's disease suddenly suffered an attack of nausea, dizziness and violent palpitation, while she was on her way to the railroad station to meet her bride-groom She had to be carried home She was very much excited and believed that her death was imminent The pulse rate rose to over 200 and was very irregular. After resting in bed with ice packs on the heart region and administration of trional, the patient became somewhat quieter

suddenly the attack ceased and the pulse rate sank to the usual rate of 120 to 130 beats per minute Three weeks later, without any evident cause, another similar attack occurred during the night After that, following improvement in most of the symptoms, the patient remained free from attacks for two years The pulse, however, usually showed pronounced irregularity Recently she again has had several attacks of palpitation, shortness of breath, and anxiety states

§6. The rhythm of the heart beat in Basedow's disease is usually regular. The sphygmographic pulse record shows a rather uniform curve in the majority of cases. In many cases the characteristic *pulsus celer* is recognizable. According to my own experience and that of several other observers, however, arrhythmia of the pulse, at least occasionally, seems to be a not unusual occurrence in the course of the disease. It can occur from time to time in connection with the other symptoms described above (see §5), tachycardia, palpitation and anxiety states.

One of our patients, the 28 year old lady mentioned above, showed considerable acceleration of the pulse—up to 120 or 130—and distinct arrhythmia S Garten recorded a pulse curve by means of a new method described by him in *Pflüger's Archiv*, *1903* Compared with the pulse recording of a normal individual, this showed that the upward curve had become entirely indistinguishable, and that, furthermore, after a series of normal pulse beats a *pulsus bigeminus* had become established While with this patient the duration of a pulse was, rather regularly, 0 5 seconds, in the *pulsus bigeminus* the time from the beginning of the first pulse to that of the second much weaker one, was 0 412 to 0 432 seconds. The duration of the whole pulsus bigeminus was 0 875 seconds

Arrhythmia of the pulse was first mentioned by Marsh (17) 1842, in the first of his cases. Germain See (417) stated that cardiac arrhythmia is a common occurrence in Basedow's disease Pierre Marie (555), on the contrary, observed arrhythmia in only one single case among eleven Kocher (2197) could recognize arrhythmia only 4 times among 80 mostly very pronounced cases of Basedow's disease It was especially noticeable in a 40 year old woman and one of 52, but even here it was only transitory. G R Murray (2553) found, among his 180 cases, irregularity of rhythm only in 12, in one case the pulse was irregular in strength but not in time intervals Arrhythmia of the pulse was discernible in only 2 out of Riedel's 20 patients with Basedow's disease (Schultze 2749) In a greatly debilitated woman of 42 strong pulsation was evident in both halves of the enlarged heart The radial pulse was weak, very rapid, and sometimes disappeared for a considerable time Another woman patient with arrhythmia presented an example of a severe case of the disease. She suffered from acute cardiac failure while on the operating table for a goiter operation Among 128 patients with Basedow's disease in Senator's medical polyclinic, Mosse (2865) found only one case of high degree cardiac irregularity This was in a 68 year old woman The arrhythmia could not be attributed to the presence of arteriosclerosis, since no other indications of arteriosclerosis could be found

Hill Griffith (658), in 2 among 26 cases in which pulse recordings were made by means of the sphygmograph, found the curve to be irregular, with very rapid and tumultuous heart action Ch Baumler (203) told of a 19 year old girl in whom even at the inception of the illness, which began upon receipt of a staggering piece of news, attacks of cardiac arrhythmia occurred as well as tachycardia at the height

of the malady. The pulse skipped every fourth beat, became again quite regular, and then declined to 80 beats.

During an acute exacerbation of all symptoms in the course of Basedow's disease in a 27 year old woman Merklen (494) observed a cessation of all heart action lasting 4 to 5 seconds Stiller (793) observed in a woman in her forties very irregular arrhythmia during an acute exacerbation and a very weak pulse of 130 beats per minute

A von Graefe (192) on the occasion of a lecture at the Medical Society of Berlin, in 1867, expressed the opinion that irregularity of heart action with increased frequency occurs in men much more often than in women In the case of the patient described above the intervals between the single cardiac contractions were extremely unlike and the force of some single contractions was so slight that no radial pulse followed v Graefe, after repeated counting of heart contractions always found 6 to 8 more contractions per minute than there were in the radial pulse No similar observation has been mentioned by later investigators, perhaps only because most of them did not pay attention to it Only P Marie stated expressly that he had not been able to find such a difference in any of his 11 cases in which he had made sphygmographic and cardiographic curves at the same time The phenomenon can probably be explained as an arrhythmia with especially weak systole which no longer makes itself evident in a *pulsus bigeminus* There is no doubt that, as v Graefe thought, such a manifestation would have an unfortunate significance because it would lead to the conclusion that a fundamental disproportion exists between the force of the heart beat and the work demanded of it

In general no harmful prognosis is attributed to the arrhythmia in Basedow's disease On the other hand Kroug (2700) sees in a decline of the pulse rate accompanied by exacerbation of the Basedow's disease a *signum mali ominis* which demands special attention on the part of the doctor since this may indicate organic changes in the myocardium

§7. Only a small number of reliable studies of the behavior of *blood pressure* in Basedow's disease are available According to P Marie's (555) measurements on two patients with Basedow's disease, the blood pressure was unaltered However, the figures given by him, 170 mm mercury on the art radialis while lying down and 140 mm when the lower arm was held free, indicate, rather, an elevation of the blood pressure.

According to Basch,[1] who has made numerous studies with his sphygmomanometer, the blood pressure in the *art radialis* registered between 100 and 140 mm mercury, an average of 120 mm in healthy men of middle age He gave 150 mm as the upper physiological limit Federn[2] found the blood pressure in the *art radialis* somewhat lower, 80 to 90 mm mercury out of an unusually large number of measurements undertaken by him with the same apparatus It could rise temporarily to 100 mm or more in healthy persons Sahle,[3] on the other hand, using the sphygmo-

[1] Der Sphygmomanometer und seine Verwendung in der Praxis, Berliner klin Wochenschr, 1887, No 11, S 179 und Praktische Winke fur den Gebrauch und die
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manometer of Basch, usually recorded higher readings, up to 160 mm and more, in the *art. radialis*. According to G Olivier's measurements[4] of blood pressure the *art. radialis* taken with Hawksley's sphygmomanometer, where a solid rod is used to stem the pulse, a reading of 90 to 100 mm while in a recumbent position, and 100 to 120 mm while sitting or standing, was recorded for normal persons With the Riva-Rocci sphygmomanometer, which shows several improvements over that of Basch, Sahli (l c. p. 130) obtained median values of 150 to 160 mm for normal persons G. Gärtner[5] recorded readings fluctuating between 90 and 100 mm in healthy persons, using his blood pressure apparatus, the "tonometer" (in which the degree of pressure at the moment of the flow of blood into the fingertip, previously emptied of blood, is determined by its cyanotic coloring, thus utilizing our most delicate perceptive organ, the sense of sight Hugo Weiss[6] gave 120 mm as the median figure *for the blood pressure in healthy men, 100 mm for women and, as lowest limit, 90* for the former and 80 for the latter.

I have cited the above account, which could be duplicated many times, in order to indicate the rather wide range, physiologically, within which the *blood pressure varies, without considering the differences in results obtained* by using various types of apparatus. Care must therefore be taken, in considering the blood pressure in Basedow's disease not to draw general conclusions from individual cases, especially since the mental state may alter the blood pressure to a considerable degree, and the mental condition plays an important role in Basedow's disease

H. Weiss (l c.) sometimes obtained very high tonometric readings in studying the blood pressure in healthy persons, following mental excitement In a few cases he found a rise of 30 to 40 mm, probably, he believed, resulting from a stimulation of the vascular nerves and the consequent raising of the peripheral resistance G Kapshammer[7] also reported similar observations The fluctuations were especially great in nervous as well as hysterical persons During operations performed without narcosis he observed a rise of 50 to 60 mm

Using P. Marie's measurements, Hill Griffith (658) tried to determine the arterial tension in 26 cases of Basedow's disease In 10 cases he reported that it was normal (38 46); in an equal number it was abnormally low He found it above normal (23 08%) in only 6 cases Figures for the blood pressure were not given. In the majority of the cases, in which the disease had *run more than a year it ranged below the category for the normal or* lower tension.

Demargne (2181) gives the readings of arterial pressure obtained with the use of Potain's sphygmomanometer in 12 patients with Basedow's disease They lie between 120 and 190 mm. In the majority of the cases, including some severe cases, they did not rise above the normal limit

[4] The clinical aspects of arterial pressure, Edinburgh med Journ , 1898, November

[5] Über einen neuen Blutdruckmesser (tonometer), Wiener med Presse, XL, 1899, No 26

[6] *Münchener med. Wochenschr , XLVII, 1900, No 3, S 67*

[7] Wiener klin Wochenschr , XII, 1899, No 51, S 1279

With the Riva-Rocci apparatus S Garten obtained readings which fluctuated between 150 and 160 mm in a 28 year old woman patient The measurements of a healthy, vigorous man of about the same age showed the same readings. Federn also, according to a written communication to Donnath (2281), found a rise in the blood pressure in all cases of Basedow's disease. Sittman (1917) was able to determine the rise in blood pressure in 2 cases. In both of these, the autopsy showed hypertrophy of the left ventricle with the valves normal

L V Schroter (2344) on the other hand, measuring the blood pressure with the Gartner tonometer, obtained the abnormally low reading of 85 mm in a 25 year old woman patient, with Basedow's disease Klein (2393), according to Riva-Rocci, measured a blood pressure of 170 mm in the *art radialis*, with a pulse of 124 beats per minute in a 50 year old woman with severe Basedow's disease

Haskovec (2290) *believed* that he could distinguish a relationship between blood pressure and exophthalmia In 6 cases with no exophthalmia, or with only slight signs of it, the blood pressure fluctuated between 85 and 120 mm In one case with no exophthalmia the blood pressure was, on the other hand, between 85 and 120 m In one case with considerable protrusion of the eyes a blood pressure of 145 to 150 mm was found, which, three weeks later decreased to between 100 and 110 following an almost complete disappearance of the exophthalmia

G F. Suker (2769) found a pulse of 140 beats per minute, a blood pressure of 150 to 170 mm, and once even of 200 mm in a 35 year old very near sighted Negro woman with Basedow's disease It is not stated how these measurements were determined Intraocular bleeding occurred in both eyes and Suker regarded this as caused by the high arterial tension

We are indebted to Spiethoff (2235) for a large series of blood pressure measurements in Basedow's disease which he made at the Jena Polyclinic on 20 cases, usually with the Riva-Rocci sphygmomanometer, as modified by v Recklinghausen. These showed that blood pressure was not always altered into the one direction In severe cases a rise in blood pressure as well as a fall occurred, while in less severe cases the blood pressure did not deviate significantly from the normal In one case, classified as rather severe, a *blood pressure measurement could be taken daily for nine successive* days Here, only a relatively slight fluctuation of blood pressure appeared A definite relationship to the pulse rate could not be determined J Donath (2281) made blood pressure measurements of a still larger number of patients with Basedow's disease. The results gained from repeated determinations made on 9 patients, using v. Basch's sphygmomanometer, showed mainly normal or somewhat elevated blood pressure, seldom a decrease, using for comparison v. Basch's median value for the *art radialis* (see above). Testing 17 patients with the Hawksley sphygmomanometer he

recorded subnormal pressure readings almost as often as above normal readings and only three normal readings. Using the Gartner tonometer *pressure readings made on 15 patients, readings in some cases frequently* repeated showed a reduced pressure (51 to 81 mm) in two cases, and in 6 cases an increased pressure (135 5 to 158 mm) assuming as the normal limit 90 to 130 mm of mercury.

The results of the numerous measurements made by J Donath on 41 patients with Basedow's disease agree, on the whole, with the conclusions of Spethoff that the blood pressure in such patients may be either reduced or normal or increased In a minority of cases it is reduced In the majority it is normal or, just as frequently, increased

Fr. Kraus (2912), making his measurements by means of the Riva-Rocci apparatus with the v. Recklinghausen improvements, discovered that the blood *pressure in patients with Basedow's disease undergoes great fluctuations* but is by no means as greatly increased as, *for instance*, in patients with arteriosclerosis, indurative nephritis, etc The readings in the individual cases ranged between 85 and 195, 90 and 215, 70 and 170, 80 and 155, 90 and 175, 80 and 200, 85 and 145, 120 and 190, 90 and 195 mm In determing the precise blood pressures in Basedow's disease the condition of the heart must be taken into consideration as well as the state of the vasomotor system, which may vary greatly in different vascular regions

§8. *In milder cases a physical examination usually will show no deviations* from normal. In severe cases of the disease, however, auscultatory as well as percussion changes often take place

§9. Very frequently, the heart sounds are especially loud, particularly the first sound at the apex of the heart Often a humming murmur can also be heard. The murmers are usually systolic and distinguishable as softer or [illegible] whistles, sometimes perceptible over the whole area of the heart, usu[illegible] base but in many cases also over the apex

[illegible] of his 49 cases, [illegible]

Among 80 cases of Basedow [illegible] ported by A. Kocher (2197), murmurs were recognized [illegible] n two thirds of the total number of the cases, 26 times over both apex a[illegible] usually more distinctly over the latter, 16 times only at the base, 5 times only over the aorta, twice over the pulmonalis and twice over both of the great arteries In 23 of the cases heart *size was found to be normal In 23, more or less dilatation was evi*dent. The murmurs were, without exception, systolic In a 23 year old man and a 32 year old woman the systolic whistle near the heart occurred only during tachycardia attacks (see above §5). *In 19 cases the absence of sounds is expressly men*tioned In two of these a dilatation of the heart to the left was evident

R G Murray (2553) has found murmurs quite often among his 180 cases of Basedow's disease In 26 of these a systolic murmur most distinct over the right *ostium venosum*, was heard In 19 cases it was loudest over the cardiac apex, and in 18 cases over the apical and pulmonary region In 45 cases no murmur could be heard and in 72 cases no mention of it was made

In half of the 80 cases about which W Gilman Thompson reported (2773) murmurs were heard In many cases these disappeared under treatment

According to Fr Muller's observations (2718) systolic murmurs over the *pulmonalis* and intensification of the second pulmonary sound is frequent. In a few cases a murmur was heard over the cardiac apex during diastole. Also, sometimes a murmur can become audible during systole, occasionally, it may disappear entirely (Leube 315 and 337). The murmurs have the peculiarity of frequently changing in intensity, or, indeed, of sometimes ceasing entirely, only to commence again later. It is just this changeability as well as their final disappearance under treatment or cure of the patient which makes it evident that in such cases no serious alterations have occurred in the ostia or valves

Traube (145) believed that these sounds could be explained by a weakness of the heart muscle due to an anemic condition of the patient, because of which the degree of tension in the valves and walls of the large arteries, necessary for the production of a sound is not attained In a number of cases the explanation of Friedreich (191, p 310) must surely apply, that the murmurs are produced because of a relative insufficiency of the valves caused by the existing cardiac dilatation The murmurs at the arterial ostia must, according to Friedreich, be attributed to an irregular vibration of the walls of an aorta which has also become enlarged Since systolic murmurs can be distinguished also in cases where dilatation of the heart cannot be demonstrated and can, in fact, be definitely ruled out, the occasional murmurs in these cases require another explanation. They may be looked upon partly as murmurs produced by an accelerated flow caused by the greater frequency of the ventricular contractions To be sure, we have no direct evidence of this, I consider it, however, not improbable that under the influence of changes in the innervation of the heart such as occur in Basedow's disease such conditions may occur. At any rate, the fact that, as we have seen, these accessory murmurs occur in many cases only during stimulated and accelerated cardiac action seems to support this view Since certain authors hold these murmurs to be anemic, it would fit in very well with this view if we consider that in severe forms of the disease anemia and cachexia are involved, producing a reduction of the arterial pressure and a reduction in the viscosity of the blood, factors which exert an accelerating influence on the outflow rate of the blood. I believe it probable, however, that another factor must be considered in the explanation of these occasional sounds, namely the influence of the muscle tone

of the heart, an important component in the production of the first heart sound. It may be assumed that the increased intensity of the heart action produces metabolic disturbances in the heart muscle sufficient even to become recognizable over the ventricle as a systolic whistle.

§10. Not infrequently, especially during acute activation or exacerbation of the disease or during its long duration, one is able to verify by percussion a more or less considerable *increase in the volume of the heart* in all dimensions, or more pronouncedly in the region of the left ventricle. Recently the Roentgen ray method has shown that the dilatation of the heart made evident by percussion often is simply caused by the increase in the diastolic volume, especially at the beginning of the disease. There are all possible intermediate stages between such a condition and dilatation or hypertrophy. As radiography and percussion make evident in such cases usually the whole heart is involved in the dilatation, though frequently the left ventricle is predominant.

Dennni (2639) calls attention to the fact that the heart of a patient with Basedow's disease is especially subject to fatigue Its reserve strength is soon exhausted and its wall yields This dilatation which affects its diameter is usually only slight and is reduced again by means of rest, although more slowly and less completely in advanced cases Occasionally the aorta is found to be slightly enlarged Parallel with this increase in the heart diameter, often discernible after only moderate fatigue, the occurrence and disappearance of the murmurs take place

Passler (1632) found that among 46 cases in which valvular disease could be entirely discounted, the heart was physically altered in 15 Usually a left sided extension of the cardiac dullness could be distinguished, but in a few cases right sided also, though to a slight degree only Systolic murmurs were heard three times at the base and the apex of the heart

Among about 80 of Kocher's cases (2197) the heart was found to be normal in 40, and in 35, chiefly those which were observed at the height of the disease, usually only a slight increase of the absolute cardiac dullness was perceptible In several cases it could be determined during the period of the observation that the dilatations were subject to fluctuation and at times were imperceptible

In 93 of his 180 cases of Basedow's disease, G R Murray (2553) noted the position in which the heart beat could be felt most distinctly In 52 cases it corresponded to the normal condition or lay somewhat median of the mamillary line In 34 it was found to be 1½ to 5 cm lateral to this line In 2 cases it was in the sixth intercostal space in the mamillary line In 2 others it was a finger's width lateral to this, and in 3 cases it lay in the anterior axillary line Death came suddenly in one of these cases where there was great dilatation of the left ventricle

In half of Riedel's 50 cases (K Schultze 2749) an increase of the cardiac dullness could be demonstrated, 5 times affecting both ventricles, 18 times only the left, and twice only the right.

It is extraordinarily noteworthy that not only in mild cases but also in those in which a definite dilatation has been recognized, the heart can return to normal size again following a disappearance of the disturbance or of the murmurs.

V. Hosslin's (1450) 22 year old patient, already mentioned, developed an acute and very considerable cardiac dilatation with hypertrophy and relative insufficiency of the valves This disappeared completely as did the loud systolic murmur at the cardiac apex when the Basedow's disease was cured H observed the same in another case But after emotional upset the dilatation of the right ventricle developed again within a few hours and the long-silenced murmur at the apex returned

Likewise, Stiller (793) tells of a very acute dilatation which appeared suddenly and developed rapidly in a 43 year old woman, resulting in a relative insufficiency of the tricuspidalis The cardiac enlargement, as well as the murmurs disappeared completely when the Basedow's disease was cured

W Gilman Thompson (2773), in 2 very severe cases of Basedow's disease, observed cardiac dilatation which appeared suddenly with loud murmurs at the apex and base and intensive palpitation in the precordial region and at the neck Following a favorable turn of the illness the cardiac enlargement as well as the murmurs disappeared after a few weeks

In a 16 year old girl with an incompletely developed form of Basedow's disease, Bradshaw (2622) found a pronounced hypertrophy of the right ventricle with none of the usual causes

In many cases of Basedow's disease a hypertrophy of the walls of both heart chambers develops But since, as we have seen, the blood pressure in the majority of the cases is not raised at all or only slightly, it follows that the hypertrophy of the heart must be traced to the acceleration and strengthening of the heart action At this time, the question of whether this is due to a toxic influence upon the heart muscle itself or to the action of the nervous system must remain moot.

§11. In severe especially acute cases, an enormous dilatation of the entire heart may develop early with systolic sounds at all ostia and with strong pulsations of the veins and, in a short time, the worst consequences such as serious valve disease (Baumler 1812) or malignant endocarditis (W. G. Thompson 2773 and others) But also, even though the dilatation may be less pronounced various severe consequences resulting from tricuspid insufficiency may occur, such as symptoms of congestion, edema, or even congestive ascites when this dilatation affects predominantly the right ventricle which usually offers less resistance.

It may well be that in severe cases the cardiac muscle is more or less insufficient because of its unusually great work load due to the enormous and continuously accelerated rate of pulsation even if greater resistance in the circulation did not have to be overcome. In addition it must also be remembered that the heart muscle is usually affected in severe cases of

Basedow's disease with the toxic chemical changes usually involved, which result in a reduction in the albumen content of the body. Also, circulatory disturbances resulting from the dilatation of the ostia and cardiac insufficiency can become critical and the myocardium may undergo degenerative organic alterations. But even without this, autopsies have shown that the heart muscle usually displays only slight, if any, pathological changes, the weakness of the heart muscle and the dilatation cause those dreaded attacks of asystole which, accompanied by cardiac dyspnea, are associated with distressing anxiety, cyanosis, congestive edema, etc.

Debove (461), Charcot (613), Broca (951), Bruhl (936), Bettman (1406), Boinet (1695), Fr Kraus (1870), Bénoit (2258) and others mentioned the occurrence of intercurrent asystole

The attacks of asystole can entirely disappear again under suitable treatment Nevertheless, the indications of the beginning cardiac insufficiency are ominous in the prognosis of Basedow's disease and it is this cardiac failure that in most cases, in which the patient dies, is the cause of his demise.

G Guillain and Courtellemont (266) made the quite unique observation that, in a case of typical Basedow's disease in a 28 year old woman, an extensive thrombosis in the system of the *vena cava superior* developed in connection with a severe asystole. Edema was present and cyanosis of the face, neck, and upper extremities and an enormous enlargement of the presternal veins of the neck etc. Autopsy showed that a persisting hypertrophic thymus gland was pressing on both of the *venae innominata* and especially on the left side But it may probably be assumed that the severe cardiac dilatation and the exhaustion of the heart muscle favored the occurrence of this extensive thrombosis.

§12. Although in isolated cases the existence of organic cardiac abnormalities can be diagnosed during life[1] such findings probably can be attributed chiefly to pre-existing lesions or chance complications, and are in no wise to be taken as inherent in the nature of the disease I call attention to the clearly recognizable part which rheumatism plays in the etiology of this disease.

§13. Together with the above manifestations a highly characteristic, and, in well-differentiated forms of Basedow's disease, unfailing sign can be

[1] Fritz (119), Greenmayer (257), Perry (290), Moutet (852, Mitral stenosis), Hirsch-Hauheim (2509), in a great number of cases Among others, J Russel Reynolds (932) did not find one case with involvement of the heart Pässler found only five among 51 cases He believes that these must be due to valvular defects

seen: dilatation and strong pulsation of the carotids, during which the lateral neck region is brought into plainly visible rhythmic movement. A finger laid on the large neck arteries can feel a definite thrill and by means of auscultation one can hear a loud, almost constant murmur which seems to be stronger at each systole. Also, the larger branches of both carotids, namely the upper thyroid arteries, show a more or less noticeable enlargement and powerful palpitation, sometimes, also, a definite thrill and in the thyroid gland itself a distinct thrill and bruit may be present, although a palpable swelling is not evident (Gehardt 2070, Druckert 2060).

This ceaseless pulsation in the large cervical and cerebral arteries is sometimes also felt subjectively by the patient, especially in the head or neck, as a troublesome throbbing A patient of Passler (1362) complained of rhythmic ear murmurs on both sides, which could be suppressed by pressure on the *arteriae auriculares poster* (see also §140).

In the small cervical and cerebral arteries an increased pulsation is usually no longer demonstrable J Schulz (2118) observed even at a distance not only the pulsation of the artery *thyreoidea superior* but also of the branches of the *art temporalis* and *maxillaris* This is certainly an exception In the very severe case of a 42 year old woman, Kocher (2197) also observed strong pulsation of the temporal arteries

Under greater force of cardiac impulse and pronounced rapidity of the pulse it sometimes happens that one can perceive a slight rhythmic shaking of the head, when in a resting position, corresponding to the rhythm of the pulse.

This is the so-called Musset's sign, sometimes observed in insufficiency of the aorta and in aneurism of the aortic arch Zeitner (2598) observed this sign in 4 pronounced cases of Basedow's disease and believed it to be among the more frequently occurring sign of this disease. Belluci (2613) attributes these rhythmic head motions to the stretching of the normally tortuous carotids and the *art vertebralis*

§14. In very striking contrast to the powerful pulsation of the large neck arteries is, in most cases, the smallness and softness of the radial pulse wave This sign caught the attention of Parry (8) and Graves (18) and has been frequently confirmed since then. The pulse often has the pronounced characteristics of a *pulsus celer*.

§15. In rare cases—and these are then usually of a serious nature—the stronger pulsation extends to other regions of the arterial system. For instance a strong pulsation of the abdominal aorta has been noted by a number of observers.

Naumann (44) in reporting a 56 year old patient, was surprised by the appearance of "an uncommonly strong abdominal pulsation" six days before the fatal outcome.

This was especially intense 4 cm from the navel. Such cases have also been reported by Stokes (46), Charcot (55), Hervieux (65), Cerf Levy (98), Laycock (158) (twice), Baumler (203), Andrews (209), Perres ... , 47 year old man (348), Dawson in a 25 year old woman with ...
Sutherland in a 26 year old woman (2...
F. W. Burton (752) tells about a pulsat...
aorta which was so strong that it coul...
(775) 30 year old woman patient the ...
the most troublesome symptom. It could only be made somewhat ...
kept her limbs continually drawn up against the body. Also, in a case reported by A. J. Campbell (2158) which took an acute course, heavy pulsation was noted in the abdominal aorta, and the pulsation in the abdominal vessels was especially distressing for the patient. Visible pulsation of the abdominal aorta was observed by F. Chvostek (1030) in a 47 year old Basedow's disease patient. Guthrie (1109) believed that pulsation of the abdominal aorta was to be seen often and even speaks of an abdominal form of Graves' disease. Among the 14 cases of Basedow's disease wh... ...ports from the Gerhardt Clinic, pulsation of the aorta ab... ...s another such case from th...
tions ...
oped severe case of Basedow's disease ...
Dinsheim (243) the aorta of a 29 year old woman pulsated ... abdominal wall, and in a 33 year old woman aortic pulsation was "occasionally" to be seen above the navel. Among 24 cases from the Gottingen Clinic, reported by Runge (2228), more or less pronounced aortic pulsation was observed four times. Pron... ...of the abdominal aorta was observed also in a 23 year old woma... ...man in the Mikulicz Clinic (Reinbach ... (2295), in a ...

In these cases an especially strong ... so could usually be observed. In a few, there w...
and of the capillary pulse as well. Fletc...
heard a loud whistling bruit over the abdominal aorta.

§16. In some cases an unusually powerful pulsation has been observed in the more peripheral arteries. In fact, according to C. Gerhardt's (1439) experience, abnormal pulsations and sounds in the smaller arteries occur fair...

(art... n

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hands without definitely distinguishable insufficiency of the *tricuspidalis* or of the valves of the veins. A relative insufficiency of the tricuspid valves, Bäumler thought, must nevertheless be considered possible (see above §11). A. Kocher (2197) found a weak pulsation of the large neck veins, not synchronized with the carotid pulse, eighteen times in 20 cases. Concerning a case of venous thrombosis in the region of the vena cava sup. see above §11.

Signs in the Thyroid Gland

§19. The second major sign is enlargement of the thyroid gland. Goiter is usually present early, even if the first beginnings often escape the observation of the patient and the doctor. The typical Basedow goiter is, in the majority of cases, only moderately large, of rather uniform shape and of soft elastic consistency. In addition there are certain peculiarities of behavior *of the blood vessels which, when well defined, must be looked upon* as especially characteristic of the disease.

§20. Nevertheless, the size of the goiter varies widely. Sometimes the swelling is so slight that it can be distinguished only by carefully directed special examination. Many patients at first call attention to the fact that their collars have become too small lately. In fact, cases occur in which even the most skillful examiner cannot find any abnormal enlargement of the thyroid gland. In many, especially new cases, the enlargement of the thyroid gland, absent in the first examination, is first found in the course of observations of the other signs. It also happens that when a thyroid enlargement is not observed, it may nevertheless be established by means of an exact investigation of the past case history that such was present in an earlier period of the disease. Furthermore, it must be remembered that during the course of the disease the volume of the thyroid gland may vary to such an extent that goiter is lacking at one time, while it may be clearly observed at other times.

In a few cases in which a thyroid enlargement could not be definitely determined by means of a clinical investigation, a slight but unmistakable enlargement of the lateral lobes was found at the autopsy. Finally it must not be forgotten that the goiter, in exceptional cases, can be located entirely or in large part within the thorax.

In most of these cases, percussion and an exact radioscopic examination *of the thorax will reveal its presence. Once in a while the retrosternal posi*tion of the goiter is only discovered by means of an operation or during autopsy (see §21 below)

To sum up all these circumstances it must be said that the entire absence

among 80 cases Kocher (2197) observed, by means of a light application of the stethoscope, a more or less loud systolic sound over the brachial and femoral arteries in a 22 year old woman and a 42 year old woman and a 30 year old man. In the first of *these cases a distinct capillary pulse could be seen through the thin fingernails on* the fingers A systolic sound over the *brachialis* and a double sound over the *cruralis*, was recognized by Kocher in a 23 year old woman In 3 cases, by means of very careful application of the stethoscope over the *art femoralis* a systolic sound was discernible which became markedly grating in character with a firmer application of the stethoscope A distinct double sound over the right *art. cruralis* was heard by Tuczek (Gause 2175) in a 59 year old woman patient with typical Basedow's disease In a number of especially pronounced cases C Gerhardt (1105 and 1439) found a double bruit in the crural artery, sounds in the *art brachialis* and, in the palm of the hand, pulsation of more distant small arteries and a capillary pulse Also, Zeitner (2598) recognized sounds over the *art brachialis* and a capillary pulse in a 47 year old woman

§17. In rare cases pulsation has been noted in the liver, the spleen and even in the kidneys

Among 14 cases in the C Gerhardt Clinic, pulsation of the spleen has been noted once, and in the liver four times, in one case certainly without dilatation of the latter organ (M Grohmann 1202) In another case from the same clinic, reported by J Maybaum (1347), strong pulsation of the abdominal aorta *was reported as well as* pulsation of the spleen and in one case, beside the pulsation in spleen and liver, uneven movements in the palatine arch could be observed which seemed like a pulsation (Gerhardt 1105) Liebert (123) observed pulsation in the liver in 3 cases of the disease and believed them to be of arterial nature, an observation which probably applies also to the majority of Gerhardt's cases of pulsation in the large abdominal organs Friedreich (191) believed that the liver pulse in his 2 cases was venous, caused by the relative insufficiency of the *tricuspidalis* A 43 year old woman with an acute case of Basedow's disease with massive cardiac dilatation, a systolic murmur, and signs of congestion was observed by Stiller (793) Systolic pulsation of the liver occurred as a result of relative tricuspid insufficiency Among *his numerous* cases Kocher noted a liver pulse only in two sisters 23 and 24 years old (2197)

§18. The neck veins also, *i e.* the jugular and the thyroid vein are sometimes found to be greatly enlarged and swollen (Marsti 17, Stokes 46, Friedreich 191, Chvostek 224, and 269, Kocher 2197, especially his very advanced cases, and others) and distinct venous murmurs could often be perceived. (Friedreich 191, p. 311, Chvostek 269, 15 observations, P Guttman 1110, Kocher 2197, in several cases) J. R Reynolds (932) distinguished *venous murmurs in the majority of his 49 cases.*

In exceptional cases, pulsation of the cervical veins can be observed Friedreich (191, p. 311) has observed this occurrence in 2 cases, and Chvostek (224) (6 observations) and Baumler (203, p 597) have observed them in one case each. In the latter, at the crisis of the disease, the distinctly visible pulse movements extended as far as the veins of the backs of the

Eales (405), Gueneau de Mussy (492), P Berger (578), Maher (669), S Snell (737), de Giovanni (830), Liebrecht (916, in a 68 year old man), H Mackenzie (918), Demme (964), Stierlin (1077, in 2 out of 3 cases; in 3 the right half was the more affected), G F Johnston (1120), Abram (1259), P. Fridenberg (1308), Armaignac (1683), Bonnet (1695), Miller (1755), Cahen (1828), Terson (2242), Kroug (2700, twice among 5 cases of one-sided thyroid gland swelling, out of a total of 106 cases), Donchin (2641, in 2 out of 46 cases)

Cases in which only, or predominantly, the left lobe was enlarged were reported by Richardson (197), E Fraenkel (305, first determined by autopsy), Payne (562), Saundby (637), Lang and Pringle (667), Hammar (767), Petersen (1234), Berndt (1405), Devay (1560), Fujisawa (1965) and von Kroug (2700) (in 2 out of 5 cases of one-sided goiter)

Statistics of several observers concerning symmetrical or asymmetrical forms of the goiter in Basedow cases are instructive in this connection.

Hill Griffith found a bilateral goiter 16 times among 32 cases and in 3 among 16 cases it was more developed on the right side (That is in 18 75% of bilateral goiter) The right lobe was enlarged only twice In 14 cases it was stated that no goiter could be discovered

S West (686) noted 15 among 38 cases in which the thyroid swelling was unequal, and moreover it was always more pronounced on the right side, in 2 cases only the right side was enlarged In 4 cases it was learned from the statements of the patients that the right side had shown a swelling first Among 6 cases of Kahler's (7750) the goiter was nearly symmetrical 4 times, and twice it was larger on the right than on the left Of 47 cases reported by Mannheim (1222) there was one in which no discernible goiter was discovered during the whole duration of the disease Four times no goiter was discernible any longer at the time of the examination Seventeen times among the remaining 42 cases it appeared nearly equal on both sides, 8 times the right was larger than left, 13 times it was prominent on the right side only, 3 times the left was larger than the right, and once only was the left side larger Among 17 of von Ditisheim's cases (1293) goiter was absent once, 5 times the right lobe was more enlarged and twice the left Among 49 cases collected by von Clarke (1546) the goiter was fairly symmetrical 39 times, 9 times the right lobe was larger and once the left one Of 9 cases reported by Ehrich (1915) from the Rostock Surgical Clinic, moderate enlargement involved both of the two lobes in 8 cases In 2 of these cases it was larger on the right than on the left In a 32 year old woman patient the left lobe was transformed into a tumor the size of a goose egg H Moses (2864) who used, partly, the same material, found among 24 new cases of Garre's that the goiter was rather symmetrically developed in 21, and the right lobe chiefly affected only in 3 patients Of 18 typical cases of Basedow's disease from von Mikulicz Clinic, as reported by Rembach (2010), the goiter was symmetrical 9 times, 5 times the right lobe was larger than left, 3 times the swelling was confined chiefly or entirely to the left side In these cases it was a matter of fist-sized or larger than fist-sized tumors and a tumor had already been present long before the appearance of the Basedow's disease The patients did not come from goiter regions Only in one case was the goiter larger on the left side than on the right among the 20 cases which J Schulz (2118) reported from the surgical department of the Hamburg hospital, the goiter was nearly symmetrical in 4 cases In 9 cases the right lobe was larger, in only 4 was it actually goitrous In 2 patients the left lobe was the more voluminous and

of thyroid enlargement throughout the entire course of Basedow's disease is rare, to say the least (see §239 below).

This much is certain, the size of the goiter and the severity of Basedow's disease bear no direct relation to one another.

Sometimes the Basedow goiter may attain considerable size. But even in such cases the swelling of both lobes of the gland usually does not greatly exceed the size of a goose egg In most cases, the size of the Basedow goiter falls far short of those monstrous forms which are so often seen in the neck region And if such an enormous swelling is found it is in persons in whom a goiter has already been present for shorter or longer time, sometimes since youth, and the symptoms of Basedow's disease appeared later (so-called secondary Basedow's disease) (see §243 below).

Among 147 cases of Basedow's disease in which G R Murray (2553) recorded the size of the goiter, 51 were described as slight if the swelling could be distinctly felt by palpation of the gland, although they sometimes had escaped the notice of the patients; 58 times it was described as moderate if it was plainly to be seen as well as felt, 29 times as considerable and disfiguring In one case the goiter was of enormous size The circumference of the neck reached 60 cm In 8 other cases the presence of a thyroid enlargement was not evident at the time, although in 5 of these, according to the statements of the patients, goiter had previously existed

It would certainly be desirable, especially in connection with the frequent variations in the volume of the goiter, if the size were given in terms less vague than "slight," "large" or "pronounced," etc or if the size of the gland lobe were indicated by comparison with a walnut, an apple, a goose egg or a fist, etc A uniform procedure would have insured more definite statements of the measurements J. A. Hirschl (2675) offered some suggestions on this subject which deserve consideration First, as far as possible, the height and breadth of the isthmus and the lobes should be reported in centimeters In measuring the circumference of the neck, place the number 20 of a tailor's measuring tape on the spine of the vertebra and then bring the shorter part of the measuring tape around the neck toward the left of the circumference and the longer part toward the right After tightening the measuring tape slightly, loosen it enough so that the neck is not constricted and measure during a pause after expiration

§21. While a fairly uniform symmetrical swelling of the lower anterior neck is the typical form of Basedow's goiter, nevertheless a preponderant enlargement of one lobe is a very common occurrence. As already noted by Graves (18), Stokes (46) and Trousseau (128), it is usually the right lobe which shows the greater enlargement. It also sometimes happens that only one lobe is enlarged while the other is either not at all, or only slightly swollen. In a majority of such cases the location of the goiter is on the right side.

Such observations have been reported by von Egeburg (34), v. Graefe (192), Eulenburg (226), Chvostek (269, 15th observation), Patchett (275), Féréol (303), Roesner (340), Yeo (396, became enlarged on the left side only after two years),

Eales (405), Gueneau de Mussy (492), P Berger (578), Maher (669), S Snell (737), de Giovanni (830), Liebrecht (916, in a 68 year old man), H Mackenzie (918), Demme (964), Stierlin (1077, in 2 out of 3 cases, in 3 the right half was the more affected), G F Johnston (1120), Abram (1259), P Fridenberg (1308), Armaignac (1689), Boinet (1695), Miller (1755), Cahen (1828), Terson (2242), Kroug (2700, twice among 5 cases of one sided thyroid-gland swelling, out of a total of 106 cases), Donelan (2644, in 2 out of 46 cases)

Cases in which only, or predominantly, the left lobe was enlarged were reported by Richardson (197), E Fraenkel (305, first determined by autopsy), Payne (562), Saundby (637), Lang and Pringle (667), Hammar (767), Petersen (1234), Berndt (1405), Devay (1560), Fujisawa (1965) and von Kroug (2700) (in 2 out of 5 cases of one sided goiter).

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in one case (of a 21 year old woman) only the left lobe was transformed into a compact, fist-sized swelling Among 80 cases of Kocher's (2197) the goiter appeared extended evenly over both sides 43 times, 25 times it was more on the right side than on the left and it was more or less diffuse, and 5 times it was developed on the left side only In 89 out of 120 cases of G R Murray's (2213 and 2553), an account was given of the shape of the goiter Usually the swelling was rather symmetrical but occasionally the right lobe was larger than the left Only 6 times among 180 cases (2553) was the left one larger In 2 cases the enlargement affected only the right lobe. In one the isthmus was included The left side was the location of the swelling only once, and in one case an enormous fibro-cystic goiter was described which had been present for a long time In all of the 80 cases summarized by W Gilman Thompson (2773) the thyroid glands were more or less enlarged, in most of them only slightly and rather symmetrically In 14 cases the swelling on the right side exceeded that of the left, and in 9 the left was larger

Among 95 cases observed by myself, an approximately symmetrical development of the goiter occurred in 52 cases, and in 8 of them no goiter was discernible Once it was developed only on the right side, 31 times it was larger on the right than on the left, in 3 others it was more developed on the left side

A survey of these cases leads to the conclusion that in about a third of all cases the right half is preponderant.

It may be well to add the observation here that a survey of the accounts given by the anatomists dealing with the normal condition of the thyroid gland shows them to be fairly unanimous in stating that the right lobe of the thyroid gland is usually larger in all its dimensions than the left This is stated by Henle in his *Hand buch der systematischen Anatomie des Menschen*, Vol I, p 646 (1897), *Anatomie des Menschen*, Vol II, p 538 (1866). Rauber, also, in *Lehrbuch der Anatomie* confirms the observation that the right lobe is usually a little wider and longer than the left While Testut in his *Traité d'anatomie humaine* (1894) gives no description of the differences in volume between the lateral lobes, Chr Simon in the *Traité d'anatomie humaine publié sous la direction de* P Poirier, T IV, p 568 (1898) states that the right lobe is generally more voluminous than the left Also, E A Schafer & J Symington make the statement in Quain's Elements of Anatomy, that the right lobe is generally somewhat larger in all dimensions than the left In several of their illustrations (especially fig 319, p 311 and fig 323, p. 312) this is plainly apparent.

Nodular goiter forms, *strumae nodosae*, as well as cellular degeneration of the goiter, appear rarely in Basedow's disease. These arise only when the goiter has been present for a long time, and was there already sometime before the appearance of the Basedow symptoms. An exceptional occurrence is retrosternal goiter, which has been observed a few times in Basedow's disease.

Heinlein (1584) found this in a 41 year old woman who suffered from attacks of tachycardia, violent tremor, and very great difficulty in breathing, likewise Goris (1969) described it in a 15 year old girl in whom no neck tumor could be found although the laryngoscopic examination indicated the presence of an intrathoracic goiter. In O'Carrol's case (2106), in a 20 year old woman, hardly a trace of goiter

could be felt on the neck but in the autopsy a large intrathoracic goiter, reaching as far as the aortic arch, appeared. Sokolowski (2138) mentioned briefly a case of Basedow's disease in which little could be felt of the thyroid gland, and where, upon operation, a large deeply ingrown goiter was discovered In the Greifswald Medical Society Minoski (2517a) showed a patient in whom, for several months past, tachycardia, exophthalmia, tremors, and a pronounced emaciation has been conspicuous Nothing of the thyroid gland was observable in its normal location A more careful examination, however, showed that the larynx lay rather deep, the ring cartilage was not far above the upper sternal margin and rather close above both collar bones one felt the tips of the two horns of the thyroid gland An example of a so called submerged goiter (goître-plongeant) The x-ray photographs showed faint shadows on both sides of the *manubrium sterni*.

§22. The texture of the typical goiter in Basedow's disease is soft or more or less firmly elastic. In the early stages of the development of the goiter the thyroid gland usually feels soft. After prolonged existence it often becomes harder. In exceptional cases the goiter can become quite firm in the later stages, especially in those rare cases in which the symptoms of myxedema are added (see §221 below). In those atypical forms mentioned above (see §20) of the goiter in which it is of an unusual size and often also irregular and knobby in form, as in endemic goiter, the most varied degree of texture is found. In the early stages of the disease a sensitiveness or painful condition of the swollen thyroid gland is noticeable

§23. Those manifestations primarily differentiating the goiter of Basedow's disease from ordinary goiter are, beside the enlargement and the strong pulsation of the goiter swelling itself, the sounds and the whirring bruit which can be heard and felt over it more or less distinctly These manifestations which Kocher grouped together under the name of vascular-goiter signs are by no means evident in all cases or at all times But if they are all present together or singly, as, for instance, is often the case in the incipient stages, they must be considered especially characteristic of Basedow's disease.

§24. A rhythmical up and down movement of the entire goiter by the continuing powerful pulsation of the carotids may very often be found in a Basedow's goiter by placing the hand upon it This transmitted or up and down movement is, however, not to be confused with that which results when the numerous enlarged arteries of the gland pulsate as far as the smaller branches and produce a rhythmic expansion movement of this gland, which is enclosed in an elastic capsule. This latter form of pulsation, the expansive pulsation, assumes special significance when it is discovered. Trousseau (1281) already distinguished very clearly between the two kinds of pulsation of the goiter and compared the latter type with the pulsation

of an aneurysm That a pulsation of the thyroid gland may occur in Basedow's disease even if a goitrous enlargement is not evident has already been briefly mentioned above (§13).

In a 39 year old woman servant with cardiac palpitation, rapid pulse, shortness of breath, feeling of exhaustion, shaking, and slight protrusion of both eyes, C Gerhardt (2070) found noticeably strong pulsation in the neck, chiefly centering about the thyroid gland, although an actual goiter was not evident Over the arteries of the gland a whirring sound could be heard In this case, there was also a distinct pulsation in the liver and the spleen Drugbert (2060) has described a case of Basedow's disease in a 24 year old man in whom the thyroid gland did not appear enlarged, yet pulsated distinctly

A pulsating swelling can develop also in goiters which have been present for years if a Basedow attack occurs (Demarres (43), Gros (85), Fournies and Oliver (190), Poesner (340), Rehn (2009) in a 47 year old woman, Kocher (2197) in a 35 year old woman and others

On the other hand the pulsation can, in the later course of the disease, disappear at the time that the goiter hardens

§25. A stethoscope placed upon the goiter often detects a more or less loud buzzing murmur, chiefly systolic, or if continuous, apparently intensified during systole The intensity of the murmur is often unequal over different parts of the goiter, loudest, usually, above the entrance point of the large thyroid arteries, especially the upper one, and often, in fact, to be found only here Sometimes, there is only a soft systolic whistling *bruit* which requires the most careful attention. in certain cases, on the other hand, the blowing sound is so loud that it is almost as great as that from an *aneurism varicosum* P Guttman (1105) considers this arterial goiter *bruit*, already well known to Trousseau (128) and very carefully described by V Dusch (404), to be very important diagnostically in distinguishing goiters which are not caused by Basedow's disease. In the latter a sound is never heard, because such goiters do not show the uneven enlargement of the arteries which, with the hypertrophy, are chiefly concerned in the production of arterial sounds in Basedow's goiter In these, however, the arterial goiter *bruit* is never absent in the course of the disease. As we shall see, neither of these signs are universally applicable. Nevertheless, the arterial goiter *bruit* can be held to be a valuable diagnostic aid, especially in cases lacking one or another of the diagnostically important signs

§26. The thrill which digital palpitation of the goiter demonstrates clearly in many cases cannot always be felt over the entire surface, but sometimes only at the entrance point of the upper or lower thyroid arteries

Heinlein (2835h) has expressed the opinion that the thrill occurs because, under increased cardiac action, the arterial wave of blood is forced into the enlarged, delicate and thin-walled blood vessel lying close beside the artery, and the blood flowing through the enlarged *vena thyroidea* is thrown into a kind of whirling motion This is especially true of the *vena thyroidea sup* The physical origin of the thrill would thus be analogous to the origin of the same phenomenon in *aneurysm arteriovenosum* except that the open communication between the two vessels is absent

§27. Numerous enlarged bluish veins often show through the skin on the surface of the goiter, but are seldom as distended as those found in voluminous simple goiters Sometimes enlarged tortuous arteries can also be observed pulsating on the surface of the enlargement.

§28. Concerning the relative frequency of vascular goiter signs, instructive disclosures have been made on this subject by observers who have paid special attention to these phenomena.

Kocher (2197) demonstrated an expansile pulsation in 41 77% of his numerous Basedow cases Bruits were detected in all but 11 out of 75 cases about which exact descriptions are available, that is, in 85 33% In 2 of the 11 cases lacking a bruit, the goiter pulsated In one of these a thrill also could be felt, and in the 9 others at least a strong pulsation of the considerably enlarged thyroid arteries was demonstrable

Among 14 of the cases collected from the Gerhardt Clinic by Grohmann (1202) the arterial goiter sound clearly occurred 8 times and in 9 cases the pulsation was distinctly noticeable In the 47 cases which Mannheim (1222) collected at the Mendel Polyclinic goiter *bruits* were recorded in 27 Only in 12 cases a systolic blowing or whirring *bruit* was observed, in 15 the absence of this symptom was specifically emphasized But it must be remembered that most of these cases were under observation for a short time only O Kahler (775a) noticed distinct goiter *bruits* in all 6 cases reported, and furthermore a conspicuous thrill in 2. Ditisheim made the same report in this matter for 9 cases of the 17 cases from the Zurich Medical Clinic In 3 cases a loud systolic blowing was noted, in 1 a thrill at the same time, in 1 case a pulsation was noticed and in 5 cases the absence of vascular signs of the goiter was especially noted Among 9 cases reported by Ehrich (1959) from the Rostock surgical clinic, thrills and murmurs were mentioned in only 3 Among 20 cases described by Schulz (2118) from the surgical division of the Hamburg Hospital, the presence of pulsation is noted in only 3 In one of these cases a loud blowing sound was heard over the goiter In 2 cases there was a considerable *bruit* without pulsation, and in 2 a definite thrill could be felt when a hand was laid upon it

In 96 of the 120 cases of G R Murray (2553) descriptions of vascular goiter symptoms are given In 63 patients *bruits* could be heard over the goiter, and in 41 these coincided with the systole In 19 cases there was a continuous venous *bruit* which, in 10 of them, became distinctly louder with every systole A thrill could be felt over the goiter in 25 cases. Among Dock's (2644) 32 cases a systolic sound over the goiter could be recognized in 26

Among 24 cases of Garre's, H Moses (2864) found that in 10 there was pulsation, or thrill, or both together, and in 3 systolic *bruits* over the goiter together with a perceptible thrill Riedel (Schultze 2749) demonstrated "in the great majority" of

his operatively treated Basedow cases an abnormal involvement of the blood vessels which had already clearly been evident from the clinical examination In milder cases this showed itself by perceptible pulsation of the goiter and by vascular sounds, in severe cases a hand laid upon them felt a distinct thrill Often there was a rhythmical enlargement of the whole gland, the expansie pulsation of which could be directly observed These symptoms were described as troublesome and frightening by many patients

Senator (1148) considered the arterial *bruit* in the goiter as not at all constant Mobius (2717) admitted that the *bruits* were characteristic in that they occurred only in the Basedow goiter but remarked that they also were often absent, at least temporarily The statement of Russell J Reynolds (932), based on his reports on 49 cases, is that vascular *bruits*, synchronized with the pulse, could be heard over the goiter in Basedow cases That this, however, is only an exceptional occurrence, even when distinct *bruits* could be heard above the carotids and the cardiac apex as well as over the jugular vein, is certainly not a generally acceptable statement. In direct contradiction Th Kocher (2197), who had opportunity to observe more than 3000 goiters, and who has precisely examined the thyroid glands of a great number of patients with Basedow's disease from various countries, has established the thesis of "no Basedow's disease without vascular goiter"

Although, as shown in the above summary and confirmed by numerous other reports in the literature, pulsation and bruits are absent in quite a number of otherwise entirely typical cases, this may still have its cause partly in the fact that these symptoms often undergo conspicuous variations during rest as well as during periods of remission of the disease If it has passed its climax they may decrease considerably, and even the abnormally extensive and heavy pounding of the large thyroid arteries may disappear completely. In the more unusual cases in which the goiter is hard or filled with nodules or cysts, a rhythmic rising and falling of the entire swelling can certainly be observed, but expansive pulsations and sounds as well as thrill are usually absent.

§29. A special peculiarity of Basedow's disease closely related to the vascular sign just described is the fact that in many cases it is possible to reduce the goiter swelling considerably by means of an even pressure or, indeed, sometimes to make it almost disappear. But sometimes only part of the goiter shows this peculiarity and in some otherwise very pronounced cases such a diminution of the goiter cannot be brought about to a noticeable degree H B Gladstone (2181) has made an observation demonstrating strikingly the emptying characteristic and thereby the essentially vascular nature of the thyroid enlargement in many cases of Basedow's disease. If such patients, while lying on their backs in bed, with all pillows removed, are told to raise the head and look at the feet without any other aid than the use of the neck muscles, the disappearance of the goiter, resulting from the stretching of the neck *fascia* is observed at once This

phenomenon can certainly be used to advantage in differential diagnosis, but it is quite as inconstant a sign as the arterial goiter *bruit*. In agreement with this are the facts that the goiter swelling of Basedow's disease is often found at post mortems to be smaller than it was in life, or indeed it may have disappeared entirely. It is known to the surgeon that after ligature of some or all of the four thyroid gland arteries the volume of a Basedow goiter decreases at once to a noticeable degree and sometimes by as much as half

On the other hand Fr Kraus (1870) has called attention to the fact that an inconspicuous diffuse thyroid enlargement becomes distinctly noticeable to sight and touch and a strong beating of the thyroid arteries can be brought about if such a patient is directed to increase the intrathoracic pressure by "inflation", with mouth and nasal apertures closed Upon release of the pressure the swelling is reduced to its former lesser volume

It may be well at this point to remember that, although there are goiters with conspicuous vascular signs which have no connection with Basedow's disease, Lücke (390) has already pointed out and emphasized the peculiar fact, about such pulsating goiters, that they are observed primarily in youthful individuals, and that they show a swelling, indefinitely outlined which encompasses the entire thyroid gland more often than only one of its lobes, is of soft consistency, and is susceptible to reduction in size under slow pressure The goiter *pulsans acula* represents only a transitory stage, either it decreases again or an ordinary parenchymatous goiter develops from it Wölfler also (1019, Part II, p 90) looks upon the simple vascular goiter as rare and cites as such a case described by von Pietrikowski[1] However, this seems to have been, rather, a swelling of cavernous structure Likewise Wetts (1053) called attention to the rare occurrence of vascular goiters Among the numerous cases he operated upon, von Riedel observed only two of these, one in a 20 year old man and one in a 21 year old girl In both cases it was parenchymatous goiter with extraordinarily numerous blood vessels, especially enlarged veins, not only on the surface, but also in the body of the goiter A Kocher (2197) reports from his father's clinic a number of case histories of vascular goiter in which it is shown that the vascular goiters vary among themselves, some being large, soft pulsating goiters with degenerative characteristics, containing greatly enlarged veins, and some being smaller, diffuse, hypertrophied, soft goiters with pronounced alterations in the intensity of the vascular signs The first form occurs more often at an advanced age, and almost entirely in the goiter regions, the latter occur, on the other hand, chiefly in younger individuals, sometimes even before puberty The case histories recounted by Kocher demonstrate clearly a certain relationship and transition between vascular goiter and Basedow's disease In 3 cases, beside the characteristic vascular indications of the goiter, symptoms are described which are peculiar to Basedow's disease, i e , acceleration of the pulse in some, in a few cases exophthalmia, in others tremor and increased perspiraton. Another case concerned the 18 year old son of a woman who had been a typical Basedow patient and had been cured by an operation The son had, at the time of puberty, developed a small goiter which subsequently caused attacks of respiratory distress Besides a

[1] Prager Med. Wochenschr. 1882, No. 9.

vascular goiter [illegible]

We shall have occasion later to refer to this case and similar ones

§30. After explaining the important role which the special nature of the blood vessels plays in thyroid enlargement in the disease with which we are concerned, a better understanding is gained of the very peculiar characteristic distinguishing the goiter in Basedow's disease: the frequently observed variations in the volume of the goiterous swelling during the course of the disease It can increase either following mental stimulation or without any evident cause, it increases usually at the time of menstruation, where even in a normal state a slight swelling of the thyroid gland has repeatedly been found (Moutet 852) On the other hand the size of the goiter has been seen to diminish at times of fear, shock and similar influences These variations can be so considerable that at certain times a thyroid enlargement is recognizable and at other times not

Such cases are mentioned by Moutet (852), Bradshaw (951), A Maude (1226a), Murray (1483) (2553), H Mackenzie (1881), S West (686), Fr Warner (2032) and Llewelyn Jones (2301) In the cases of the last three observers the goiter, previously evident, diminished, while the other symptoms of Basedow's disease remained.

in combination with similar variations in heart action and in the other disease symptoms

This was conspicuously the case in the 3 observations which Graves (12 and 18) reported, as well as in the cases of Marsh (17), J Begbie (29), Romberg and Henoch (39), Gildmeister (136), v Stellwag (235, 1 case), Emmert (255), Moutet (852), Bradshaw (951), L. Jacobsohn (1739), G R Murray (1483 and 2553)

During such paroxysms the vascular goiter signs above described become distinctly noticeable, even when they are only slightly evident or absent at other times. In exceptional cases the thyroid enlargement may rapidly increase so that it leads to danger of choking, and symptoms may develop requiring surgical interference

Trousseau (219) had an opportunity for such an observation in a 14½ year old boy and Roberts (363) in a 27 year old woman who was two months pregnant Shingleton Smith (418) told of a 20 year old woman who choked to death in spite of the performance of a laryngotomy A 30 year old patient of Bristowe's (648) who began to suffer from cardiac palpitation, with protrusion of both eyes, and a swelling in the neck which had been noticed 2½ years earlier, and who had suffered recently from several attacks of shortness of breath, succumbed to such an attack as a consequence of asphyxia, because timely surgical aid was not given The post mortem showed

that the goiter had overgrown the trachea and esophagus Montgomery (905) told of a 35 year old woman who had suffered from Basedow's disease for several years and whose neck measurements had shown considerable variations (between 48 and 57.5). One evening she suddenly suffered an attack of violent dyspnea, soon lost consciousness, and died in spite of a tracheotomy The right lobe of the thyroid gland had pressed upon the wind pipe and this had resulted in a softening of the cartilage A similar case was described by W G Spencer (1007) a 20 year old girl suddenly suffered an attack of extreme dyspnea and in spite of a tracheal operation performed through the upper part of the thyroid gland tumor, died a few hours later Here, too, the goiter had grown entirely around the trachea and extended a short distance back of the *sternum* down into the chest cavity Also, in a 20 year old patient about whom Steinlechner (1514) reports, the goiter showed very conspicuous vascular signs The windpipe, overgrown from both sides, caused such a shortness of breath that tracheotomy had to be resorted to at once Purulent bronchitis and lobular pneumonia with a general collapse ended in death four weeks later

Only very exceptionally does a typical goiter in Basedow's disease produce dyspnea by tracheal stenosis, in such cases it grows around the windpipe from both sides backward, more or less completely, or it extends into the thoracic cage (see §21, above). If the symptoms of Basedow's disease are combined with other forms of goiter, pressure symptoms may result just as in simple goiter.

In a woman suffering from severe Basedow's disease with a large substernal goiter, chiefly in the region of the parasternal line, Heinlein (2291) observed a varicosity extending to the right half of the wall of the thorax We shall have to deal later (§179) with another form of dyspnea which is not unusual in Basedow's disease

A peculiar condition of the goiter was shown in a case reported by V Hosslin (1450) In the 22 year old patient already mentioned several times, the thyroid enlargement diminished noticeably in size during the tachycardial attacks (see §5, above) and, in fact, in direct ratio to the severity and duration of the attack In the most severe paroxysms, lasting several weeks, and followed by a high degree of exhaustion, the formerly enormous goiter disappeared entirely, growing again after the end of the attack At the next tachycardial attack, the swelling once more was reduced After recovery from the Basedow attack, the thyroid gland was still much larger than during the tachycardial attacks

The Eye Signs

§31. The third in the series of major signs, exophthalmia, is the least regularly occurring one It is lacking in more than 20 per cent of the cases, and it develops, usually, as the last of the major signs It is, however, undoubtedly present, even if to only a slight degree, or it can be determined with certainty that it has occurred previously from the account

given by the patient Thus it must be considered a highly characteristic manifestation of the disease under discussion.

§32. The protrusion usually affects both eyes equally, although it is not unusual to find one eyeball protruding more than the other.

In 76 out of 95 cases which I have observed myself, a more or less pronounced exophthalmia was present, and in 62 of these cases the degree of protrusion could be exactly measured with the exophthalmometer described by Birch-Hirschfeld.[1] By this means it was shown that in only 15 cases both bulbs protruded equally above the temporal orbital margin In 47 cases differences were distinguishable, however, in 27 cases these were quite small (1 mm or less), 14 times they were from 2 to 2 5 mm, 3 times from 3 to 3 5 mm and in 3 cases the exophthalmia was present only on one side (right), 29 times the right bulb protruded further and 18 times the left one In 16 cases of unequal protrusion the goiter on the corresponding side was also more developed, 7 times this relationship was reversed and, in fact, in 5 cases, with greater protrusion of the left side, the right lobe of the thyroid gland was more enlarged In one case, in which the exophthalmia was greater on the right side, an enlargement of the thyroid gland could be observed only on the left side, because the right half of the goiter had been removed surgically a short time before In 22 cases the goiter was symmetrical, in 3 cases entirely absent

Among Kocher's (2197) numerous cases the exophthalmia was equally pronounced on both sides in 32, in 3 it was greater on the right, and in 3 on the left In 5 of these last 6 cases, the goiter was more developed in respect to its vascular signs on the side of the more prominent eyeball In the one exceptional case the exophthalmia was greater on the right than on the left, and the goiter was present only on the left side, since the right thyroid lobe, which probably had been greater in the first place, had been removed elsewhere by operation, unsuccessfully with respect to the Basedow's disease This therefore only seems to be an exception Among 49 of the cases assembled by Clarke (1546) the right eye was more prominent in two instances and the left one in two W Bowman (513) mentioned that he had often seen an unlike degree of protrusion of the bulbs in Basedow's disease In one case of Carrington's (651) the exophthalmia, very pronounced on both sides, was even more pronounced on the right In one case, reported by Audersch (1393), the left eyeball protruded noticeably more than the right

It happens at times that the exophthalmia occurs over a longer or shorter period on one side only, and later appears on both sides

This was already observed once by v Basedow (23, page 772) In a man, about 50 whose interesting case history Prael (67) reported, only the right eye protruded at first (the goiter affected the whole thyroid gland) Only a few weeks before death, the left eyeball also protruded greatly In a case of von Rugh (176), that of a 24 year old man, only left-sided exophthalmia existed for years, until 2 days before death, when the other eye reached an equal degree of protrusion In Hutchinson's case (312) five or six months after the occurrence of left-sided exophthalmia, the right eye also protruded, although never as much as the left. A perceptible goiter

[1] Ein neuer Exophthalmometer, Klin Monatsbl f. Augenheilk. XXXVIII, S 721, 1900.

was absent. A case of this sort, which is interesting in several ways, was observed by J. Burney Yeo (396). In a 35 year old woman a high degree of exophthalmia developed at first on the left side while the goiter involved only the right thyroid gland lobe, two years after the appearance of the protrusion of the left eye, coinciding with an exacerbation of the general condition, the right eyeball came into prominence, although never as much as the left one, and the left thyroid lobe became enlarged, without, however, reaching the size of the right one What is more, after the occurrence of the left-sided exophthalmia eyebrows and eyelashes of the left side began to fall out, and, after the right bulb became prominent the eyebrow and eyelashes of this side as well as the hairs of the right armpit gradually fell out In a young girl with incomplete Basedow's disease (goiter was absent) Samuelsohn (442) found for a long period that there was only a right-sided exophthalmia which here was the initial symptom Only later, after the general condition had grown noticeably worse, did a protrusion of the left side become noticeable In a case of Tapret's (483) the left eye first protruded, and only very much later the right one In a young woman with a temporary, moderate thyroid swelling about which Fitzgerald (541) reports, only the right eyeball protruded at first, two years later, after it had gradually withdrawn again, the protrusion of the left eye began In a 16 year old patient of Jendrassik (665) first the right bulb, and a few months later the left bulb protruded Dauschar (820) tells of a 32 year old man in whom exophthalmia of the right side occurred seven months later than that of the left, and then attained an unusual extreme In a 28 year old woman described by Volkel (945) a strong protrusion of the left eye was first observed, 11 months later the right one began to protrude Also after a while the left one retracted a little, so that at the time of the report the rather slight exophthalmia was more prominent on the right than on the left

In a 47 year old man, a patient of Gérard Marchant's, (Herbert 1973, page 151) a left-sided exophthalmia was the first sign After one year a protrusion of the right eye developed, which soon reached a greater degree than that on the left, and only after two years the further symptoms of Basedow's disease developed swiftly one after another. A woman patient of A Trousseau's (2245), related that at first only her left eye protruded, and only after this diminished again a protrusion of the right side developed, at the time of the examination an exophthamia of the right side only was found In one of Kocher's (2197) numerous cases, that of a 39 year old doctor, the exophthalmia arose first on the left side and one month later on the right Pribram (2727) told of an 18 year old girl patient who displayed an enormous exophthalmia on the right side as well as a pronouncedly vascular goiter After all the Basedow signs had decreased considerably, the girl suffered a relapse, this time with protrusion of the left eye Then she was permanently cured

On the other hand cases have been observed in which an originally bilateral exophthalmia became unilateral during the subsequent course of the disease

Thus J Russell (605) tells of a 16 year old girl in whom, after the retraction of the right eye, only the left one continued to protrude much A similar observation was made by A Trousseau (2245) on a 38 year old woman

Of special interest are those cases in which, after operative removal of one half of the enlarged thyroid gland and the accompanying reduction of the other Basedow's disease symptoms, the protrusion, which previously

had occurred on both sides disappears on the operated side, while persisting on the other. Fr Muller (2718) had an opportunity to observe such a case and Th. Kocher (2693) several times saw a reduction of the exophthalmia on the side of the operation, following partial goiter removal.

§33. Exophthalmia can also remain confined to one side during the whole course of the disease, or, at least, during the period of observation.

One-sided exophthalmia is mentioned in one case, but rather incompletely described, by Sichel (22), in 1 case each by Schnitzler (163), Mauthner (412), Baldwin (575), Dreyfus-Brissac (615), Taylor (794), in 2 cases each by S Snell (737) with suppuration of the cornea, and by G A Berry (807), in 1 case each by Williams (1522), and Bernoud (1533), and in 1 of 49 cases collected by Clarke (1546), in 4 of 39 cases which Wilbrand and A Saenger (2033) observed (in 12 no exophthalmia was present), and in 5 out of 58 cases of Mooren (1759) Hill Griffith (658) noted unilateral exophthalmia 7 times among 32 cases collected from the clinics of Little and Glascott, 4 times affecting the right eye and 3 times the left one Passler (1362) found among 51 carefully observed polyclinic cases 5 with temporary or continued exophthalmia of one side, and this always the left side Fr Muller (2718) mentioned, from his extensive experience with Basedow's disease, only 2 cases of unilateral protrusion of the eyeball In one of these cases the goiter was also onesided, and the exophthalmia affected the same side on which the goiter was located Among a total of 106 observations and 45 cases in which Kroug (2700) found exophthalmia, it was unilateral 14 times, and of these 10 times left sided and 4 times right sided Once, in a case of unilateral goiter it was on the opposite side Frank Billings (2806) observed one sided protrusion only twice among 42 cases in which exophthalmia occurred Among my 76 cases with exophthalmia it was unilateral 3 times, each of them on the right

Demarres observed, in the case of a 30 year old woman, a protrusion affecting only the right eye, together with an unusually great elevation of the upper lid Similar observations were made by W Makenzie (49 and 57, obs 269), Prael (67) in a 15 year old, a 19 year old, and an about 20 year old girl, Eulenburg (226) in a young woman with swelling almost entirely in the right lobe, also by Emmett (255) and in a 17 year old girl with a goiter strongly developed on both sides equally, Chvostek (269) (15 observations) in a woman of 55 in whom only the right half of the thyroid gland was greatly enlarged, later other symptoms appeared, confined entirely to the right side (see below paragraphs 168 and 222), Rosner (340, 3 cases) Yeo (396, 2nd case, concerning a 23 year old girl), Eales (405) in a 22 year old patient with swelling of the thyroid on the right side only (the protrusion of the right eye had been present for 8 years), Abadie (451) in a 28 year old woman with a small symmetrical goiter, Gluzinski (468), Gueneau de Mussy (492) (the goiter and periodic
choreiform movements w ... d
girl, and in a man with ... e
those of P Berger (578) u ...
ing, Saundby (637) in left sided goiter, Maher (669) in a 34 year old man with goiter affecting chiefly the right side, S Snell (737) in a 45 year old woman (exophthalmia and only very slight swelling of the neck), de Giovanni (830) in a right-sided goiter, J. A Hirschl (1208) in a 51 year old man, Baylac (J Faure 1305) in a 40 year old woman, Jacoby (E Fridenberg 1308, p. 167) in a 33 year old woman with predomi-

nantly right sided goiter, Risley (1375) in an incompletely developed, somewhat doubtful case of a 22 year old girl without demonstrable goiter, Boisseau (1606) in a 62 year old woman, Boinet (1695) in a 28 year old woman with typical glandular swelling of the right side only (also a tremor more distinct on the right than on the left), Miller (1755) in a young woman with enlargement of the right thyroid lobe only, Fere (1962) in a 50 year old woman, Witherspoon (2355) in a case of goiter of the right side only, Terson (2242) in a 60 year old woman with a goiter confined to the right thyroid lobe and a 48 year old man with no demonstrable goiter Additional cases are those of A Trousseau (2245) in a 42 year old woman, in whom the one-sided exophthalmia together with tachycardia, was the only noticeable symptom during a 3-year period, and in a 52 year old woman, who had suffered from Basedow's disease for 25 years Also, there are reports of A Barkan (2610) of one case in which the exophthalmia came to a rapid development, Gifford (2666) in a 29 year old woman in whom the onesided exophthalmia with strongly pronounced lid signs, nervousness, and occasional cardiac palpitation comprised the only disease symptoms during a long period, and finally Pfibram (2727) in a woman with a very severe illness, which ended in recovery

Mooren (317) observed exophthalmia confined to the left eye only in a 23 year old girl, and O Becker (453) reports a 28 year old woman whose exophthalmia occurred only at intervals P Marie (555) reports a 46 year old man with very slight thyroid swelling, Land and Pringle (667) report a 49 year old woman in whom the left thyroid lobe was more enlarged than the right, S Snell (737) cites a 23 year old girl, Barilla (1171) a 31 year old man without discernible goiter, Hitschmann (1209) a 36 year old single woman without a trace of goiter, P Fridenberg (1308) a 24 year old woman with a slight but distinctly palpable swelling of the right thyroid lobe and the isthmus, Hinshelwood (1732) a 24 year old girl (the small soft goiter involved both lobes), Armaignac (1689) a young girl with a swelling of the right thyroid lobe, Cahen (1828) a 51 year old man with goiter on the right side, Fujisawa (1965) a 41 year old patient of the Ziemssen Clinic (during a relapse of Basedow's disease with renewed growth of the gland remnant of the left side, a goiter operation on the right side had been performed almost two years before), Guibert (2185) a 56 year old woman, Terson (2242) a 33 year old woman without a palpable thyroid, Llwelyn Jones (2301) a 23 year old girl, Bistis (2262) a 35 year old man and a 30 year old and a 47 year old woman (in all three cases without perceptible enlargement of the thyroid) Campbell Posey and W C Swindels (2423) a 22 year old woman with moderate sized goiter of symmetrical form The one-sided exophthalmia was the first symptom of illness which she noticed after a severe fright Guttman (2280) found in a woman patient left-sided exophthalmia, eyelid signs and thyroid swelling only on the left The heart and pulse were normal at the time of the observation No complaint of cardiac palpitation had been made In a patient examined by Franke (2372) exophthalmia and eyelid signs were found only on the left side Goiter, acceleration of the pulse (80 to 88) and tremor were only slight A 23 year old woman patient of E Stern (2441) showed exophthalmia and lid signs only on the left side

A number of the cases described remained under observation until the disappearance of the condition without the occurrence of a protrusion of the other eye. The occurrence of unilateral exophthalmia in Basedow's disease is, therefore, by no means very unusual, as assumed by several authors According to the above mentioned summaries of Clarke, Wilbrand and Saenger, Mooren, Hill Griffith, Pässler, Kroug, Frank Billings and my

own, it could be calculated at about 10%. However, the count is still relatively small and chance is not excluded The total number of all cases of one-sided exophthalmia which I managed to find in my literary research came to 109, 46 were on the right side, 40 on the left, and in 23 there is no mention as to which side In the cases in which exophthalmia was one-sided for a shorter or longer time before the protrusion of the other eye occurred, it appeared 5 times on the right side first and 9 times on the left side. In cases where the eyes protruded unequally the right side usually protruded more. de Wecker (870, p 921) maintains that, as a rule, the right eyeball protrudes sooner and to a greater degree and extreme unilateral exophthalmia usually affects the right eye Buschan (1181, p 330) makes a similar assumption These statements evidently contradict the facts Furthermore, Buschan is of the opinion that exophthalmia and goiter in general keep pace with the affected side and the degree of development. Gowers also (1042) states that in unilateral exophthalmia the goiter is usually larger on the side of the protrusion. At the twenty-third Congress for Internal Medicine, Fr. Muller (2718) also expressed the opinion, based on observation of two cases of unilateral exophthalmia in which the goiter, also unilateral, lay on the same side, that an influence of the unilateral or predominantly enlarged thyroid lobe on the eye of the same side must be assumed. Reference was made to a case already mentioned above in which, after a unilateral goiter operation, exophthalmia on the side operated upon disappeared entirely, but persisted, together with the lid signs, on the side not operated on. Kocher was able to verify this observation on the basis of his wide experience. Certainly, the supposition that such an influence actually exists is very alluring Let us see, then, what the factual material shows in this respect.

Among 43 cases of one-sided exophthalmia on which exact reports about the condition of the goiter are given, the unilateral or predominant thyroid swelling was on the same side as the protrusion of the eye 17 times In 6 cases a criss-cross relationship was observed In 2 cases the symmetrical form of the goiter was expressly emphasized, and in 13 cases the thyroid swelling was quite small or not perceptible at all In the crisscross occurrence of goiter and exophthalmia the thyroid tumor affected chiefly the right lobe in the majority of cases (4 to 2)

To be sure, in unilateral goiter and unilateral exophthalmia, correspondence with the same side occurs more frequently. It cannot be questioned that in many cases the enlarged thyroid lobe may have a certain influence on the eyeball, perhaps through the agency of the *sympathicus*. But any fixed relationship is definitely excluded as shown by the crossed type, as well as by observations of unilateral exophthalmia with symmetrical or absent goiter. If in cases of unilateral exophthalmia the other signs of Basedow's disease are little developed or when, occasionally, a unilateral exophthalmia

appears among the first signs of illness, diagnostic difficulties may develop This actually occurred several times.

§34. The protrusion occurs, with few exceptions, directly from front to back in the direction of the orbital axis Exceptions to this are found in complications of Basedow's disease with ophthalmoplegia (see §127 below)

§35. In regard to degree, the exophthalmus can be disproportionate Its degree stands by no means in direct relation to the severity of the illness or to the intensity of the other signs A high degree of exophthalmia can occur among otherwise very slightly developed signs and vice versa, and pronounced exophthalmia sometimes persists when the other signs of disease have nearly disappeared While the protrusion in many cases scarcely exceeds the physiological limits, in others it is so great that a more or less broad rim of the sclera appears even below the cornea The closing of the lids is no longer possible, or only partly so, and the eyeballs are not entirely covered even in sleep To be sure, in such cases a simultaneously existing retraction of the upper lid plays a rather important part in this occurrence (see below §43) Murray (2553) observed such a patient during sleep The eyes were directed straight forward and the free edge of the upper lids reached only to the upper borders of the medium-wide pupils It happens in exceptional cases that the bulb, with the slightest stimulation, becomes displaced in front of the lids

Trousseau (219) cites Pain's case in which dislocation of the eyeball followed after an acute exacerbation of the protrusion Dauscher (820) observed an unusually high degree of exophthalmia in a 32 year old man in which the bulbs were no longer covered by the upper lids and the right was nearly dislocated In a case of the disease following a trauma in a wood-worker of 62 about whom Zimmerman reports (1166), the exophthalmia was so great on both sides that the bulbs seemed dislocated and the eyelid was almost completely raised In a man with pronounced Basedow's disease whom Rehn (1242) observed, the protrusion was so enormous that, when touched, the eyeballs became dislocated Deschamps and Perriol (1558) tell of a case of incomplete dislocation of the left eyeball where necrosis had caused the cornea to disappear In a case of Basedow's disease observed by Tucker (2889b) the bulb was displaced in front of the lid opening

As a rare instance, a case of Mason's (671) should be mentioned here concerning a woman of 40 with conspicuous Basedow's disease and very great exophthalmia, upon the approach of a hand toward her eyes the eyes reddened, and when a finger touched the upper lid, the eye, "with a sudden spasm," pushed outward still further, and became displaced in front of the lids

These enormously high degrees of exophthalmia are, in general, quite rare. Concerning the goggle-eyed patient, the physician is in many cases dependent upon statements of the patient or those around him. Sometimes,

too, photographs taken earlier can supply information. Since even slight changes in the position of the eyes change the expression of the face they do not easily escape a moderately careful observer Under certain circumstances it may be really hard to decide whether a pathological prominence of the bulbs exists or not, since even under normal conditions the position of the eyeball studied in relation to its projection through the sclerotic capsule in an imaginary frontal tangential plane from the outer eye socket, is subject to quite large individual variations The measurements taken with our exophthalmometer showed differences of between 12 and 19 mm The median obtained from the total of all repeatedly controlled measurements was nearly the same for both eyes and was about 14 5 mm

In A Kocher's (2197) measurements, executed on 250 almost entirely healthy individuals, the values vary between 8 and 19 mm (we assume as median 15 mm for the right eye and 16.5 mm for the left).

I must admit that Kocher is entirely correct when he points out that the form and width of the lid opening influence our judgment as to whether an eye is to be considered exophthalmic or not Eyes whose prominence approaches nearly the maximal physiological degree do not always give the impression of exophthalmia if the lid opening is not at the same time unusually wide, and on the other hand eyes may give the impression of exophthalmia in cases where the prominence exceeds only slightly, or not at all, the physiological median, but where the lid aperture opens wider (see §43 below).

In 64 out of 76 of our Basedow cases in which exophthalmia was present, median values in the case histories have been recorded from a series of measurements taken In 41 cases in which the exophthalmia could be described as slight, moderate or distinct, values between 15 and 21 mm, with the median 18 mm, were found In 23 cases of great or extreme exophthalmia values between 22 mm and 31 mm were found and an average of 23 mm is recorded

The case of a 78 year old stout but not really obese man with *cataract senilis* of both sides and in whom the vertex of the cornea projected 27 mm beyond the outer orbital margin of the only slightly myopic eyes, shows that a very high degree of prominence of the bulbs, approaching the maximal degree which I found in Basedow's disease, can occasionally be approached in exophthalmic eyes by means of entirely physiological conditions In another patient suffering from glaucoma the slightly myopic bulb projected 26 mm beyond the outer eyesocket margin and the upper lid showed at times a more or less pronounced retraction, the lid aperture extended sometimes 11 mm and sometimes up to 17 mm A lag of the upper lid in blinking could not be observed Any indications of Basedow's disease were absent The extraction proceeded without difficulty in both cases, and the curative process ran its course without a bandage, simply under the protective screen, and took no longer than usual.

If the Basedow patient is suffering from intense nervous excitement and is restless, difficulties may sometimes arise in attempting to obtain reliable measurement with our exophthalmometer. In such a case one must wait until the patient has calmed down. This can usually be accomplished by means of suitable treatment. The value of exact ophthalmometer measurements seems to me to be chiefly the record they provide of the changes in degree of protrusion which occur in the course of the illness. These also assure a more reliable judgment concerning the influence of therapeutic and surgical treatment.

§36. The degree of exophthalmia is subject to variations, often quite considerable, like those of the goiter and of the cardiac palpitation and sometimes running parallel with them.

Prael (67) reports that in one of his patients of approximately 50 years, the right eye, which at first was the only one protruding, "simply looking like a large goggle eye, came to project so far that the eyelids no longer could cover it completely."

It can also happen that the exophthalmia appears only at times, or, having existed for a shorter or longer time, disappears again while the other signs remain.

A. Kocher (2197) reports one such case. In a 27 year old lady the exophthalmia was noticed as one of the earliest signs but was absent at the time of the observation. Also in 3 of G. R. Murray's 180 cases in which the exophthalmia was lacking, it had been present in an earlier period of the disease.

In a man of 38 observed by F. Chvostek (400) a slight prominence of the right bulb was said to have been present for only two days. (It seems to me not entirely ruled out that the observer had been deceived by variations in the width of the lid aperture.) A merely temporary protrusion of the left eye was observed by O. Becker (453) in a 28 year old lady. In Geneau de Mussy's case (492) the right eye protruded distinctly only during choreiform attacks. In a 21 year old woman suffering from Basedow's disease and recurring mania, observed by Savage (568), a pronounced exophthalmia occurred at every manic attack, but disappeared almost completely in the intervals. Hummel (935) tells about a 19 year old girl and a 33 year old woman with otherwise well-developed symptom complexes in whom the exophthalmia was present only periodically. A 52 year old woman whom E. Berger (1088, p. 108) had opportunity to observe, noticed, after she had undergone a violent attack of cardiac palpitation five years previously, that at first the eyes protruded only during menstruation. Little by little the exophthalmia became constant. Later, it showed a variation in degree. Among 51 of the carefully recorded polyclinic cases of Passler (1362) exophthalmia was observed only temporarily in 3 and, as a rule, concurrent with a general intensification of the illness. A. Kocher (2197) tells of a 32 year old man whose eyes protruded only during tachycardial attacks (see §5 above) although otherwise there was no exophthalmia with concurrent intensification of the tremors. G. R. Murray (2213) mentioned a case in which, during attacks of migraine, the goiter became swollen and the eyes more protruding. In 3 of Riedel's 50 cases (Schultze 2749) the exophthalmia varied greatly in intensity. A 20 year old woman made the observation that her eyes protruded more a few days before the commencement of

her periods Then, with the onset of flow, the eyes receded again from their former position In a 38 year old patient observed by Caro (2812) a very conspicuous exophthalmia and the v Graef's sign occurred at times

Abram (1259) made the interesting observation that the exophthalmia disappeared during a violent attack of diarrhea, and returned again afterwards

Jules Voisin found, as Blottiere (1536) reports, that if one presses hard on one lobe of the goiter the eye on that side will protrude This protrusion, slight as it may have been, was observed not only by the doctor but was also perceived by the patient and lasted as long as the pressure continued

By slight pressure with the open hand the eyeballs can, in many cases, namely when exophthalmia has not existed very long, be returned to their sockets, but after the release of the pressure they again reach their former degree of protrusion Sansom (937) made the observation in one case that the exophthalmia disappeared when the lids were closed and that it seemed very conspicuous when they remained open. The upper lid was sharply retracted (see §43 below)

That all influences restraining the flow of blood from the orbits cause a greater protrusion of the eyes and, in fact, to a greater degree than is the case with healthy persons, we can demonstrate imperfectly on one of our patients, a 19 year old girl. A Birch-Hirschfeld tested the effect of compression of the facial vein and forward flexion of the head on the position of the eyeballs, using his helmet apparatus fitted exactly to the shape of the head with a fixed light-weight camera attached, as described in this book.[1]

This experimental arrangement permitted two profile exposures of the eyes to be made, in which all the contours overlapped exactly except the contour of the anterior surface of the cornea, which appeared double, corresponding to the change in position of the bulbus The projection of the corneal vertex of both eyes beyond the outer orbital margin amounted to 27 mm with the head in upright position Such a double exposure was made with head upright, first without compression of the facial veins, and secondly with such compression These exposures were made with a rubber-padded lead ring, exactly fitted to the head form, held firmly in place by bands and gauze bandages Upon compression, the protrusion of the bulb registered about 1 3 mm Since, in normal individuals with head in upright position (about 0 3 mm) the application of like pressure produces only a minimal protrusion, this protrusion of the bulbus in our patients with Basedow's disease must be described as very noticeable. It has been pointed out that in Basedow's disease with strong exophthalmia the facial veins, even with the head in upright position, also serve to carry the venous blood away from the orbits, while, under normal conditions, this is bound to be the case only when in a forward flexed position (see Birch-Hirschfeld, l c., p 37).

Similar exposures were made to demonstrate the effect of compression

[1] 2 Part, Vol XI Chapt XIII. p 34, 1907

of the facial veins in a forward flexed body posture. The corneal contours were then no longer parallel but approached each other. From this it is shown that the eye has moved not only forward but slightly upward. The measurement of the forward change is 1 mm at the center of the lid aperture and at the upper lid margin 1.4 mm, that of the upward movement is 1.2 mm. The result of this second experiment shows also that the result of the compression of the facial veins in forward bowed-head position in our patients with Basedow's disease is not greater than that with the head upright. Since a long continuation of the compression and forward flexion is very unpleasant for the person experimented upon, it could unfortunately not be determined with the patients whether longer continuation of the experiment would result in further increase of the exophthalmia. Experiments with normal persons permit this assumption, however, unless one wishes to assume that in exophthalmic eyes the factors acting to produce a retraction, especially the great tension of the rectus eye muscles, prevent a further protrusion.

A third observation using such multiple exposures showed the contours *of the corneal surface* with head upright, with forward flexion *without compression* of the facial veins, and with compression. In comparison with both of the first experiments these last observations make evident the influence of head flexion This is shown by a relatively slight protrusion of the eyeball (of about 0.9 mm) When, now, the flexion is added to the compression of the facial veins, the bulbus of our Basedow patient pushes forward a further 1.4 mm This added protrusion is, no doubt, due to *venous congestion in the orbits*, while the increase of the exophthalmia in forward flexion alone results, *in* part at least, from the weight of the eyeball, although here a greater fullness of the orbital veins from impedance of flow toward the *sinus cavernosus* must be taken into consideration.

The comparison of these results concerning the protruding eyes of patients with Basedow's disease, as obtained from the same series of experiments as *those with normally placed eyes teaches: 1) that in both normal* and exophthalmic eyes a compression of the anterior venous paths of outflow from the orbits *produces* a definite protrusion of the bulbus and 2) that, although this *protrusion* of the eyes *in normal* persons *only happens with forward head flexion, in the exophthalmia of patients with Basedow's* disease, even with upright head position, a compression exerts a noticeable influence 3) The absolute measurement of protrusion following compression of the facial veins in healthy persons and in such patients is pretty much in agreement. Bending of the head only, without compression of the vein, in both cases produces an *immediate* protrusion of the eyes and, indeed, *in* the exophthalmic *ones* only slightly more than in the normal The difference is about 2 mm

§37. By auscultation with an air cushion described by von Donders (253, p 102), H Snellen discovered in a case of Basedow's disease a *bruit* above the eye which he took for a vascular sound corresponding to the placental sound, but with less systolic intensification. Since such *bruits* occur only in those places where the blood channel has become enlarged, Donders believed he could interpret the sound discovered here as direct evidence of the enlargement of the blood vessels of the orbit Later Schonfeld (504) reported a patient having murmurs synchronous with the pulse, which, however, could be perceived also in other places—on the head, on the forehead, and over the mastoid process. Carrington (651) mentions a more or less continuous murmur which he detected in a 23 year old patient with Basedow's disease by auscultation above the eyeballs; it was loudest during the systole and confined to the region of the orbital aperture. Drummond (702) spoke of a weak sound which was audible with the stethoscope placed over the bulbus, but which could not be heard in the region around the orbit

L de Wecker (870) p 922, said in his *Traité* "upon auscultation of the optic region a systolic blowing sound is said to be audible which, however, the majority of clinicians have not been able to verify (*bruit reste introuvable pour la plupart des cliniciens*)" de Wecker himself, in spite of his wide experience, seems to have sought for this sound in vain. Duroziez (301) explains that the sound which he formerly believed to have heard upon auscultation above the protruding eyes is, he has become convinced, in the nature of a muscle sound. I, myself, have formerly striven in vain to discover a sound above the eyes in Basedow patients as described by Donner. On the other hand in every case it was possible to distinguish a very distinct sound if one placed the 10–12 mm sized opening of a small funnel of hard rubber over the closed lids above the bulbus, lightly but air tight, and inserted a smoothly polished perforated olive-shaped wooden nozzle, connected by a 42 cm long rubber tube from the small end of the funnel to the outer auditory canal in such a fashion that it remained fixed without having to be held in place. By means of this simple apparatus described by E Hering[1] one can easily convince himself that these sounds have all the characteristics of muscle sounds

C. Hueter,[2] evidently without being aware of Snellen's observation, described in 1878 "a very loud and deep sound" when he placed over the closed lids a voltolini stethoscope similar to the apparatus described above He covered its approximately

[1] Über Muskelgeräusche des Auges, Sitzungsbericht d K Akademie d Wissenschaften, LXXIX, 3 Abt., Februar, 1879, Wien

[2] Versuche zur Begründung einer Auskultation fur chirurgisch-diagnostische Zwecke, Centralbl f. d med Wissenschaft, XVI, No 51, S 929

33 mm wide funnel aperture with a rather tightly-stretched rubber dam. He believed that the sound from the blood stream arose not only in the capillaries of the skin of the lid, but largely also in the blood vessels of the eyeball and the eye socket. Hueter has also, however, described the muscle sound in the fingers as "whirring" and held that it was derived from the blood stream of the finger tip although Wollaston, already at the beginning of the past century, thoroughly investigated muscle sounds and very aptly compared the sounds from the finger tip with the rolling of a wagon over a stone pavement; and Brown-Sequard had recognized the sound of the finger tips as a muscle sound. Hueter's report was then taken by E. Hering as a starting point for more exact studies on the muscle sounds of the eyes. He succeeded in obtaining undeniable evidence that the sounds heard here are pure muscle sounds. That somewhat loud, rather deep clear buzzing, really almost a rattling sound which can be heard in everyone even during sleep and under light anesthesia, if the sound receiver is placed over the closed lids in such a way that it is tight on all sides, comes from the action of the lid muscles. This *orbicularis* sound may be intensified by compression to various degrees and at any arbitrary rhythm. The sound remains as long as one keeps the lids closed. If one attempts, while the funnel *rests* on one of the upper lids, to open both lids slowly so that only the free eye opens while the upper lid of the eye under experiment is held passive by means of the funnel, the sound disappears at once; or else it changes, as can be recognized by giving sufficiently careful attention and becomes, to use *Hering's* words, "like a sound coming from a greater distance." This softer continuous sound is also a *muscle sound* and originates from the tonic innervation of the eye muscle.

Brief intensifications following one another at irregular intervals may be recognized. These are caused by unintentional slight backward movements of the eyeball. They disappear, as I have convinced myself, with external ophthalmoplegia and in deep narcosis, just as, according to Hering's statements, they do in animals treated with curare. In one case of complete paralysis of the upper facial branch I missed the orbicularis sound on that side, while the steady sound became just so much more noticeable in its peculiarities. Hering has used this latter cleverly to determine the innervation laws of the eye which he has established.

As shown in the preceding discussion, the sounds which are audible over the eyes are by no means distinctive for Basedow's disease. Nevertheless, I could determine, in quite a number of patients, even with rather pronounced exophthalmia, that these sounds were especially loud and distinctly audible. This was particularly evident in a 19 year old girl with moderately severe illness, the eyes protruded 24 mm beyond the outer orbital margin. *Since in such cases both points of attachment of the portio lachrymalis* and *orbitalis* of the muscle *orbicularis* lie behind the vertex of th[illegible] that the muscle bundles describe a rather large arc when the li[illegible]vable to me that, upon simple closing of the[illegible] than that produced under normal conditions[illegible] case if, at the same time, a marked retraction of the upper lid exists[illegible]43 below). However, anyone familiar with the muscle sounds of the eyes will easily recognize that in cases with especially loud sounds, this is still merely muscle sound be-

cause. 1) it has all the characteristics of such sounds, 2) it is intensified at once by more forcible closing of the lids, and finally 3) it ceases if the eyes are allowed to open slowly in the manner described above.

In the region around the orbit the sound no longer can be heard. A weaker muscle sound, to be sure, can be made evident if one places the sound funnel over the *corrugator supercilii* or the *M temporalis* and these muscles are caused to contract.

In the patient mentioned above in whom the muscle sound could be heard especially loudly I succeeded also in detecting a sound with an ordinary stethoscope by means of an air cushion placed upon the lids, according to Donder's method. This was, however, a much softer sound, hardly distinguishable at the lid aperture. It became distinct only upon compression The peculiar buzzing character of the sound is somewhat blurred and becomes more like a murmur so that Snellen's comparison with the placental sound is certainly understandable If, however, one has an opportunity to compare directly the placental or more correctly uterine sound with the sound over the eyes, listening to the latter with a Hering sound-detection apparatus, surely the difference in the character of the two sounds will be noticed at once.

The slight systolic increase which a few observers claim to have perceived can probably be explained by the fact that in many patients with Basedow's disease a delicate, rhythmic tremor of the lids occurs when closing (Rosenbach's phenomenon, see §104 below) to which a rhythmic tightening of the muscle sound corresponds I have had opportunity to observe an increase in the disease symptoms, namely tachycardia, cardiac palpitation, and tremor at the time of an attack There was, of course, no idea of a synchronization with the systole, but it would be difficult, in any case, to prove such a concurrence, even if it existed, with a tachycardia of 120 or more beats per minute

§38. The range of movement in Basedow's disease, in contrast to that in most cases of exophthalmia, is influenced only slightly by other causes, or not at all. However, observations are not lacking, in which a certain limitation of movement in one or more directions, especially upward, and to a slight degree downward, has been determined In many cases the lateral movements could be made only with difficulty or only incompletely. We shall later (§94) concern ourselves extensively with disorders of the fixation movements. These limitations in the range of movements are on the whole to be attributed to a shift of the hinge in the movement from front to back and to the anatomical-mechanical relationship They stand, in general, in a direct relation to the degree of exophthalmia It is difficult to evaluate the extent to which anatomical changes which we shall distinguish later in the eye muscles (see the pathological anatomy of Basedow's disease) play a role in this. These limitations of movement do not cause double vision for they occur as a rule symmetrically and the maximal range of movement is usually avoided because of the ensuing discomfort Also, in one-sided or uneven protrusions diplopia does not occur unless complications occur. Motor disorders of the eyes caused by neurological disturbances

represent one of the more unusual complications of Basedow's disease. They will be discussed further on (§127).

§39. The unsteadiness of glance of many patients with Basedow's disease, their inability to hold the glance fixed, is a manifestation which already impressed Trousseau (128) (a peculiar mobility of the eyeballs) (*une mobilité étrange des globes oculaires*); it is entirely independent of the exophthalmia and is a partial symptom of the nervous unrest which is so characteristic of Basedow's disease and which is evident (see §149) in the posture of the body, the movement of the hands, the speech, etc.

§40. Pronounced exophthalmia is sometimes accompanied by a disagreeable feeling of pressure and tension. A 26 year old woman patient of Pässler (1362) had, during every exacerbation of her ailment, the feeling that the left eye was being pressed out of its socket. She did not herself notice the exophthalmia which occurred plainly on this side each time but she believed that she imagined the feeling of protrusion of the eyeball A. Kocher (2197) emphasized that 24 among his father's numerous Basedow patients spontaneously remarked upon a troublesome pressure sensation behind the eyes. Sometimes they even described it as pain In two cases this feeling of pressure fluctuated according to the changes in the exophthalmia. A 45 year old woman complained of continuous pulsatory throbbing back of her eyes This became greater with the increase of tachycardia and was always most severe in the morning.

§41. The upper lids are, in cases of rather severe protrusion, somewhat edematous and filled with bluish veins which shine through. (Concerning another form of edema of the lids see §211 below) Often, upon forcible closure of the lids, one sees the fat body of the socket bulging forward unevenly in the tarso-orbital region.

The Lid Signs

§42. Several signs of Basedow's disease which are very characteristic but definitely not constant and not always fully developed at the same time, come and go in the eyelids

§43. The most noticeable of these is a rather wide expansion of the lid aperture, caused by the retraction to the uppermost segment of the cornea and even retraction beyond the border of the cornea following some stimuli. It is not unusual, however, to find in patients with Basedow's disease, when the glance is directed straight forward, and even during very strong

illumination of the eyes, that the lid aperture is so extended as to show a narrow or wider border of white sclera remaining above the upper border of the cornea It is this sign which gives many of such patients such a peculiar expression. There is a kind of uncanny stare in the eyes and an expression of horrified astonishment or even wild fury in their glance A wide palpebral fissure creates the impression of an exophthalmia, as if a protrusion were present, where actually none exists (see above, §35). Conversely, in some of the cases in which this sign occurs a moderate protrusion of the bulbs (22 *mm. or more) may be inconspicuous.* This wide opening of the lid aperture is entirely independent of the protrusion of the eyes, it can be seen in quite a number of cases to a marked degree and, in fact, often very early in those cases in which exophthalmia is not yet present or in which, during the entire course of the disease, the position of the eyeball does not exceed the physiological measurement or does so to a hardly noticeable degree (see §47 below). Already in the earliest stage of the malady a powerful retraction of the upper lids can be observed when the patients are told to look at the doctor or at an object held before them. The retraction of the upper lid can also remain distinctly apparent after the exophthalmia has disappeared (Pedrono 632, in a 54 year old woman, A. Trousseau 2245, in a 38 year old woman and others) Within very narrow limits, however, the position of the eyeball is influenced by the position of the upper lid With the upper lid raised, the bulbus pushes slightly forward, and with the lid lowered, it retracts somewhat. This is a manifestation which has been known for a long time In some individuals it is so plainly evident that, upon careful observations of the profile, the protrusion of the eye can be perceived easily during a further opening of the lid aperture

J J Muller[1] who investigated this sign thoroughly in connection with his studies on the fulcrum of the human eye, used a clever mirror arrangement[2], described by A Fick, with which, using a suitable experimental arrangement, the eye sees its own profile reflection Muller states that, with the head in a straight position and with the line of vision parallel to the median plane, the protrusion of the bulb, during forceful contraction of the levator muscles of the lid, can be seen to increase by fully 1 mm [3] Donders (253, p 99) confirms these facts in his studies on the fulcrum of the eyes He makes use of the ophthalmometer with its axis perpendicular to the corneal axis while, with the head still, the glance on a distant point After attaching two short black hairs to the side wall of the nose in vertical position and parallel to each other, he could measure the exact distance of the latter one of the hairs by means of a doubling of the ophthalmometer image Starting from the position of the

[1] Archiv f. Opthalmologie, XIV, 3, p 183, 1868

[2] l. c , p 193. An instructive picture by E. Hering can be found in *Handbuch der Physiologie* by E Herrman, III, Physiologie des Gesichtssinnes Part 4, Der Raumsinn und die Bewegungen des Auges p. 461, 1879

[3] L c , p. 206

middle width of the lid aperture, he found that, upon widening the aperture in the middle the bulbus pushed forward about 0.8 mm, and upon narrowing it, it withdrew about 0.5 mm so that the total range of the movement amounted to more than 1 mm. The degree of the change in position varied in different persons. E. Berlin[4] discovered by means of his method, the protrusion of the bulbus to be 0.66 mm as the median measurement of 10 observations agreeing with each other. He used his subjective methods based on the apparent shifting of perspective of objects unequally distant from the eye, during direct and indirect viewing. This is the method which he used in studying the fulcrum of the eye with the eye in primary position and the lid aperture open as wide as possible. At the same time he observed a slight downward shift which amounted, on the average, to 0.63 mm.

A. Tuyl[5] who recorded directly the forward and backward movements of the eyeball by means of a lever apparatus upon a rotating smoked drum, found that with a widening of the lid aperture of 6 or 7 mm up to 14.5 mm there was a protrusion of the eye of about 0.8 mm. Varying from the average width of the lid aperture, the smallest measurement of the forward movement amounted to 0.4 and the largest 0.7 mm. At the same time Tuyl observed also a small downward shifting of the eyeball. Finally A. Ludwig[6] tried to demonstrate these alterations of the position of the eye by photographic means in a suitable series of experiments with snapshots in exact profile position, with medium and with the widest possible opening of the lid aperture. He attempted to measure them with the aid of a millimeter scale placed so that the line of vision of the eye was in the same place and parallel to the photographic plate. The measurement showed that the bulbus projected forward 0.85 mm. At the same time it seems to have descended somewhat and one sees that the lateral angle of the lids is drawn somewhat higher, the free edge of the lower lid is turned slightly outward, with simultaneous contraction of the *musculus frontalis*. Birch-Hirschfeld contributed a valuable addition to this investigation, inasmuch as he was able to determine by measurements with our exophthalmometer the occurrence of important individual differences of protrusion of the eyes during a widening of the lid aperture.

Starting from the distance of the vertex of the cornea from the outer edge of the orbit, with medium-wide lid opening and upright head position, and using as subjects of the experiments persons with nearly equal sized (emmetropic) eyes, he found that in deeply-placed eyes with an equal lid aperture (about 5 mm.) the protrusion was distinctly less and that in a slightly exophthalmic condition it was considerably more than in the medium position (about 17 mm distance of the cornea vertex from the outer orbital margin), where Birch-Hirschfeld had determined a protrusion of about 1 mm.

When there is a high degree of retraction of the upper lid with very pronounced exophthalmia, the influence of the width of spread of the lid aperture upon the position of the bulbus will exceed somewhat the values stated above. The decrease of this sign by a lowering of the upper lid, as well as by cutting the *cervical sympathicus*, will not only influence the

[4] Die mit den Augenbewegungen einhergehenden Verschiebungen des ganzen Bulbus, Arch. f. Opth., XVII, 2, p. 180, 1871.

[5] Über das graphische Registrieren der Vorwärts-und Rückwärtsbewegungen des Auges, Arch. f. Opth., III, p. 233, 1901.

[6] Beilageheft z. XLI. Jahrgang d. Klin. Monatsbl. f. Augenheilk. p. 359, 1903.

appearance of the patient favorably but it will result in a retraction of the bulbs by much as 1 mm or more. The effort to increase the retraction of the upper lid still further, to open the eye very wide, may bring about a slight additional increase of the protrusion, as shown by observation on a 48 year old man with slight exophthalmia (17 mm) but with pronounced lid signs. When he was told to do this, our exophthalmometer could determine a further protrusion of the cornea.

There is hardly any doubt that the withdrawal of the bulbus during a narrowing of the lid aperture is brought about not only by the relaxing of the levator muscles of the lid but, fundamentally, also by pressure from the contracting *musculus orbicularis*. The influence of this muscle, where it is not insufficient, will become more evident the farther back its attachments are located behind the cornea, especially the attachment in the region of the crest of the lachrymal bone, the importance of which is emphasized during the closing of the lids. I would call attention here to the observation of Sansom (937), mentioned above, who found pronounced exophthalmia in a 24 year old woman with pronounced Basedow's disease and unusually great retraction of the upper lid; an exophthalmia which was very pronounced when the eyes remained open. He saw that it disappeared when they were closed

Voluntary lid closing, even with great retraction of the upper lid, is possible in a majority of cases if exophthalmia is not unusually marked. However, it seems to require a certain effort, and one therefore often finds the lids only incompletely closed during sleep.

John Griffith (1728) described an uncommon case in a 21 year old woman in whom exophthalmia was by no means especially great, at least not greater than the other cases in which closing of the lids takes place without difficulty; yet the eyes of this woman could not be closed because of an unusually high degree of retraction of the upper lids With great effort it was possible to bring the lids to within about 4 mm of one another

A. Hill Griffith (651) mentioned a retraction of the lower lid in one of his cases. In 3 cases he found this to be simultaneous with the retraction of the upper lid. In 2 cases it affected only the lower lid upon failure of retraction of the upper. Lang and Pringle (676) emphasized expressly that they had observed so far no drawing back of the lower lid, L. Ferri (1037) said that the lower lid never shows such a retraction

I have not been able to convince myself that a retraction of the lower lid, analagous to that of the upper one, takes place. In many people, during forced elevation of the upper lid, the middle part of the lower lid draws somewhat downward, while the outer commissure is a little raised, as mentioned above. This can be recognized plainly in a diagram of A. Ludwig drawn from his snapshots taken with medium-wide opening of the optic aperture and with a maximal opening

The unusually wide opening of the lid aperture, when it was plainly apparent, was also not overlooked by the earliest observers of Basedow's disease Dalrymple, as reported by White Cooper (31), first observed this sign and clearly recognized its significance in accounting for the peculiar facial expression of the patients He attributed it to a continuous spasm of the eyelids White Cooper, (p 553) says very significantly "the eyes being greatly protruded, were nearly denuded of the protection of the upper lid by a constant and powerful spasm of the *lev palp. sup*, which drew the lid so far upwards and backwards, that much of the sclera above the cornea was visible . The expression given to the countenance by this protrusion of the globes, and the unnaturally elevated lid, is very peculiar, and the aspect is that of the wildest terror " He adds, at the same time, that this levator spasm is not unusual in nervous and hysterical women and frequently occurs in connection with other irregular muscular reactions, such as chorea

When MacDonnel (20) pointed out that in his patients the eyes seemed enlarged and had taken on an expression of staring and wild anger, and when Stokes (46) said of a woman who showed the typical signs of Basedow's disease that "the eyes were large and shining but did not protrude" they had surely observed the sign we are discussing Independent of these observers Demarres (43) very accurately described the wide-open state of the eyes It is not noticeable at first that in the horizontal glance the upper lid does not come down over the upper part of the cornea, as normally, but, instead, the cornea appears totally uncovered which gives the physiognomy a rather wild and disturbed look In extreme cases the eyes of these patients look like those of an angry person, something that is in decided contrast to the rest of their facial expression Teissier (146) emphasized that he found no protrusion of the eyes in 4 of his 5 patients who suffered from nervous excitement, cardiac palpitation, and swelling and pulsation of the thyroid gland, but that he could "only determine something noticeable in their glance" Trousseau mentions something similar (128) about a 29 year old woman who lay in his clinic in 1861 In 1863 Virchow (200, p 81 Note) gives a brief description from the case-history and the autopsy of a man who suffered from Basedow's disease and whose eyes, without being really exophthalmic, had an unusual stare and gave the impression of being enlarged de Wecker (202, p 774, Note and 870, p. 922, Note) in 1863 observed a strong retraction of the right upper lid in a pregnant woman who had cardiac pulsation but no goiter or exophthalmia The diagnosis of Basedow's disease is, however, not entirely certain here It was recognized as one of the most important diagnostic signs of Basedow's disease, and was often called Stellwag's sign only after A v Graefe (154, 192, 193) had drawn attention to this finding in 1864 and 1867, and Stellwag v Carion (235)—in 1869—had described it and studied it more exactly This designation is, as can be seen from our description, plainly incorrect and tends to give rise to misunderstandings, since we are indebted to Stellwag for the knowledge of another lid sign, the infrequency and incompleteness of involuntary blinking, which, up to that time, had remained unnoticed and which rightly bears his name If one wishes to associate the symptom of wide gaping of the lid aperture with a certain name it must be called Dalrymple's sign, according to Schneidnitz (1916).

§44. Closely related to retraction of the upper lid, but not necessarily bound up with this (see below §45) is another peculiar lid sign: a disturbance of coordination between the downward movement of the upper lid and the lowering of the plane of vision. This was discovered and described in 1854 by Albrecht von Graefe It has since been known as v. Graefe's sign.

appearance of the patient favorably but it will result in a retraction of the bulbs by much as 1 mm. or more. The effort to increase the retraction of the upper lid still further, to open the eye very wide, may bring about a slight additional increase of the protrusion, as shown by observation on a 48 year old man with slight exophthalmia (17 mm) but with pronounced lid signs. When he was told to do this, our exophthalmometer could determine a further protrusion of the cornea.

There is hardly any doubt that the withdrawal of the bulbus during a narrowing of the lid aperture is brought about not only by the relaxing of the levator muscles of the lid but, fundamentally, also by pressure from the contracting *musculus orbicularis*. The influence of this muscle, where it is not insufficient, will become more evident the farther back its attachments are located behind the cornea, especially the attachment in the region of the crest of the lachrymal bone, the importance of which is emphasized during the closing of the lids. I would call attention here to the observation of Sansom (937), mentioned above, who found pronounced exophthalmia in a 24 year old woman with pronounced Basedow's disease and unusually great retraction of the upper lid; an exophthalmia which was very pronounced when the eyes remained open. He saw that it disappeared when they were closed.

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§45. Notwithstanding this apparent relationship between the two lid signs, many cases are known in which only one of the two occurred while the other was entirely or temporarily absent. Also, when both signs occur at once they are not always equally well developed.

In the case of L. Bruns mentioned above the gaping of the lid aperture was pronounced, the correlation between lid and eye movement during the lowering of the plane of vision, however, was only slightly disturbed. After the patient's sojourn in a mountain resort the upper lid no longer lagged upon lowering of the glance although a high degree of retraction of the upper lid remained. On the other hand, Hinshelwood (1732) observed a case in which, in the course of the treatment of the ophthalmia, the wide gaping of the lid aperture disappeared, and only v. Graefe's sign persisted. Maude (1056) in several cases found one of the two lid signs distinctly developed while the other was absent. Among the cases which I observed, including 38 which showed both lid signs in 2 instances, with distinct retraction of the upper lid, the v. Graefe sign was only slightly developed, and in 4 with pronounced v. G. sign retraction was only slight, or was temporarily lacking. Three times the v. Graefe sign was completely absent, although one case showed a wide gaping of the lid, with weak retraction. On the other hand, among 21 cases with failure of retraction of the upper lid I have seen the v. Graefe sign more or less clearly demonstrated. In one of these cases, in a 19 year old girl, whom I had had opportunity to observe for a long time, it was only later that, temporarily, a distinct retraction of the upper lid appeared although the exophthalmia had not altered noticeably.

In 2 of the 3 cases of Stellwag (235) which influenced him to undertake these studies, there was a very wide opening of the lid aperture and an infrequency of involuntary blinking although the accompanying movement of the upper lid with the lowering of the plane of vision was in no way affected.

In 2 observations by P. Marie (555) on a 40 year old man and a 50 year old man v. Graefe's sign was absent during the pronounced retraction of the upper lid. The same was true in 3 cases of Hill Griffith (658) in a 25 year old woman, a 50 year old woman and a 52 year old man. On the contrary he never found the wide gaping of

[illegible]

with an enormous retraction of the upper lid it could be perceived only at times, usually it was absent. In a 34 year old man observed by Maher (669) and a 17 year old man observed by Th. Reid (677) the coordinated downward movement was not interfered with during strong retraction of the upper lid. O. Kahler (775a) observed several cases in which, with a conspicuously gaping lid aperture, the v. Graefe sign was not discernible. In the 4 acute cases of Basedow's disease described by Fr. Muller (1134) the abnormally wide gape of the lid aperture and its accompanying staring, horrified facial expression was noticeable at once, while v. Graefe's sign could be discovered in only 2 of the cases.

Retraction of the upper lid with absence of the v. Graefe sign was observed also in 2 cases by Berger (1088) and in a 31 year old male patient of Hannemann's (1319). Also in a 9 year old girl among Steiner's (1513) cases, in several among the 51 cases of Passler's (1362), in 2 among the 18 cases described by Hunerfauth (1735), in a 13 year old girl patient of Zuber's (2036), in a 4 year old boy under Vorıot's (2132) observation, in 2 among 14 cases of J. A. Hirschl (2192), in a 48 year old man with

[illegible], while the hand is moved slowly downward, the upper lid does not follow this downward movement at first, or very incompletely at the most. During a further lowering of the glance, the lid goes downward spasmodically, without, however, nearly reaching the low position which under normal conditions would correspond to the position of the cornea. I, myself, among others, have observed cases in which, with the glance directed straight forward, no retraction of the upper lid took place, so that in spite of the exophthalmia, the upper segment of the cornea was covered; only upon lowering of the glance a more or less wide rim of the sclera became visible above the cornea. If the glance is kept directed downward for a time it can happen that the upper lid, as Passler (1362) observed, follows after a while, and the visible band of sclera disappears L. N. Boston (2809) made the observation in his cases that if the patient follows the surface of the open hand with the eyes, moved downward from the upper region of the field of vision, the upper lid follows the movement for a short distance, stops for a moment and then shows a slight spastic backward movement upwards, finally following the eyeball in a further lowering of the glance

If in the lowering of the glance the upper lid stays far behind, then the bulbs, which are allowed to follow the hand which is rising, again go upward alone a little way However, upon a further raising of the glance they followed promptly, in fact, in many cases, excessively so L Bruns (1024) has especially emphasized the fact, already briefly mentioned by v Graefe (193, p 272), that a lagging of the upper lid in relation to the movement of the bulbus only occurs during the lowering of the glance, and therefore he calls this sign the inadequate lowering of the upper lid during the lowering of the plane of vision

A few more interesting observations can be mentioned which are helpful in clarifying the relation of the two lid signs to one another In one case of Ramsay's (1000) the upper lid at first followed the lowering of the plane of vision, but then, with further lowering of the glance, it remained behind and after a few seconds "a spastic retraction of the upper lid occurred" so that the sclera was exposed above the cornea. In one case of L Bruns (1024) the lid, during the lowering of the glance, lagged, only slightly, and upon elevation of the glance above the horizontal plane it went up at once to the very highest position In Passler's case (1362), already briefly mentioned, when the upper lid, which was at first insufficiently lowered, was made to follow by a longer fixation of the lowered glance, and when the plane of vision was raised again, the lid hastened upward so fast—to get ahead, so to speak, of the movement of the bulbus—that the sclera again became visible above the cornea.

lid signs to appear as one of the earliest indications of the disease and thus assume critical diagnostic importance.

In 1864 A. v. Graefe (154) demonstrated the sign described to him in a case where this sign, combined with accelerated heart action with normal heart size and valves, comprised the entire symptom complex. Also, in a male patient shown in the Berlin Medical Society in 1867 (192), the protrusion of the eyes hardly went beyond the physiological measurement and the goiter was apparently unilateral. But the upper eyelids were strongly retracted. With eyes turned downward, the upper lid did not reach over the anterior aspect of cornea in the usual manner. Moore (317, p. 15 and 523, p. 70) found a 23 year old woman lacking any trace of thyroid gland swelling. Only the left eyeball protruded. v. Graefe's sign was distinctly developed on both sides. Also, in a 28 year old woman with cardiac palpitation and a distinctly goitrous swelling, but without any prominence of the bulbs, he did not find the lid signs absent. de Wecker (202, p. 744 and 870, p. 922 Note) in 1863, observed a lady who, during pregnancy, was subject to palpitation and who, *because of an enormous gaping* of the right lid aperture, showed a highly peculiar facial expression. Goiter and exophthalmia did not develop and the symptoms disappeared again after delivery. P. Marie (555) tells about a 40 year old man in whom there was no goiter nor protrusion of the eye but, together with other characteristic signs he showed a definite retraction of the upper lids. Among A. Hill Griffith's (658) 32 cases there was a 24 year old woman without goiter and exophthalmia but with a definite retraction of the upper lids. W. Lang and J. J. Pringle (667), in their journal, describe 6 cases in which the lid signs could be seen to be very pronounced while other signs of Basedow's disease were only indicated or, it seems, not recognizable at all. Only in 1 case, a 49 year old woman, there was a slight protrusion of the left eye and a slight swelling of the thyroid gland. In a 48 year old woman the left eyeball had shown some protrusion half a year previously. At the time of the observation exophthalmia could not be determined with certainty. Heart signs could not be discovered in any of the cases at the time of the examination: a 42 year old man had had palpitation intermittently for 10 years and a 14 year old boy had suffered from palpitation as long as he could remember, both during bodily exertion and without it. It is noted, however, that the heart action was quiet in *status praesens* and there were no heart murmurs. Nervous symptoms were, in general, absent, or indicated nothing of significance. The 14 year old boy suffered from *globus hystericus* and occasional double vision.

In a young lady observed by S. Snell (737), only a nervous excitability was evident, except for the definitely pronounced lid symptoms confined to the right side. The left eye was normal in every respect. Application of direct current, tonics and a change of air led to definite improvement which continued up to the time of the final observation, 10 months after cessation of the treatment. The author does not hesitate to pronounce this an incomplete case of Basedow's disease. In a 34 year old woman in whom goiter and exophthalmia were absent, J. Seymour Sharpey (941) found v. Graefe's sign very clearly developed. In similar cases Gordon Dill (1089) found a strong retraction of the upper lid in a 47 year old man and both lid signs in a 34 year old male patient. Furthermore, Timotheef (1159) saw all the lid signs in a 49 year old woman and Terson (2242) the Dalrymple sign in a woman patient. Pässler (1363) *tells about a 62 year old farmer* who exhibited the v. Graefe sign to a very pronounced degree and also suffered from sleeplessness, persistent sensation of warmth in his head, and tendency to violent sweating. Formerly this man had

exophthalmia on the right side only and strong retraction of the right upper lid, whom Terson (2242) observed, in a 41 year old woman patient of Deshusses (2280); further, in 4 among 42 cases of Mannheim (1222) while in 8 of his cases only v Graefe's sign is noted Among 39 cases of Wilbrand and Saenger (2033) v Graefe's sign was absent while the pronounced gaping of lid aperture was present and 3 times it was present together with an absence of the retraction of the upper lids Among 12 cases of v Mikulicz (2103) the latter was present only once and v Graefe's sign alone only 3 times Among 69 cases of Kocher's (2197) concerning which lid-sign records are available, with a marked gaping of lid aperture v Graefe's sign was lacking 6 times, and in 7 cases with absence of retraction of the upper lid it was more or less distinctly evident In 7 others it is noted without any statement concerning the behavior of Dalrymple's sign G R Murray (2213) cites 20 among his 89 cases in which attention had been given to the lid sign a marked gaping of the lid aperture without any disturbance of the lowering movement of the upper lid was noted, in fact, 9 times with an absence of exophthalmia, in 9 cases with v Graefe's sign only, and once with absence of the protrusion Cases in which v. Graefe's sign only was present are also reported by Burton (752) in a 34 year old man, by Briener (1178) in 8 patients among 20 cases, and by E Berger (2146) in a 56 year old woman

§46. As is the case with the wide gaping of the lid aperture, so also the disturbed or inhibited accompanying movement of the upper lid with the lowering of the plane of vision is quite independent of the degree of exophthalmia. A. von Graefe emphasized this fact as early as 1864 (154) He also pointed out that this sign can disappear in the course of the disease, without a measurable diminution of the protrusion being demonstrable, an observation which, since then, has often been confirmed (see also above §51) At the same time he told of an interesting observation: in one case of Basedow's disease the sign disappeared temporarily after a morphine injection, while the exophthalmia showed no change On the other hand, we know that the protrusion of the eyes can diminish without any improvement of the disorder of the accompanying movement of the upper lid

Thus it was in the above mentioned case of Hinshelwood (1732), in addition, Pedrone (632) reports on a 33 year old woman and a 52 year old woman in whom, [illegible] raefe's [illegible] st, but [illegible]

§47. When exophthalmia is absent most of the lid signs are absent also. In a number of case histories this fact is especially emphasized However, many cases are known in which with absence of protrusion of the eyes the lid signs were found to be more or less plainly developed. Some of these were cases of Basedow's disease that were also otherwise incompletely developed and in which a strumatous swelling of the neck was absent or only slightly perceptible, sometimes also, no pathological signs of the heart could be distinguished at the time In such cases it is not unusual for the

in the width of lid aperture of the two eyes The right upper lid stood distinctly higher and lagged noticeably during the lowering of glance Also, the left upper lid *followed the downward-turned eye less completely than is normal Close investiga*tion showed a very slight enlargement of the middle thyroid lobe, the patient was easily excited and complained of increasing heart- and headache There was, however, neither palpitation nor acceleration of the pulse. The eyes protruded no further th[illegible]
ins [illegible]

[illegible]
potential was normal Further investigation showed that the lady had lost much weight of late, tired easily, perspired a great deal, and blushed unaccountably Definite dermographia (see below §166) could be demonstrated She also suffered from a sensation of heat to such an extent that even during the coldest seasons she preferred to wear summer clothing On climbing stairs and when excited she felt a *slight palpitation The pulse showed* 96 *to* 100 *beats per minute* Thyroid enlargement, exophthalmia, and carotid pulsations were absent, however, a tremor of the hands could be easily observed.

More frequent are the cases where, with an otherwise well developed symptom complex of Basedow's disease, exophthalmia is absent, whereas both or only one of the lid signs are well developed The previously mentioned case of Virchow's (200) belongs to this category, likewise a case each of A v Graefe and Mooren, discussed above, furthermore 4 cases reported by P Marie (555), a 25 year old woman and a 30 year old woman and a 51 year old man in whom a wide opening of the lid aperture was apparent, and a 37 year old man in whom only v Graefe's sign could be demonstrated In a 42 year old woman described by Eckervogt (516) the eyes lay deep in the orbits, but the lid aperture opened widely and the upper lid followed the downward movement of the bulbus only incompletely Wherry (743) observed in a 32 year old woman with no exophthalmia, a very marked retraction and incomplete lowering of upper lids only on the left side W R Gowas (1042) (p 260) offers the example of a woman with only a left-side retraction of the upper lid and absence of protrusion of the bulbi during the initial stage of the disease E Clarke (1185) saw very clearly developed lid signs with absence of exophthalmia on the right side and, on the left, an indication of the v Graefe sign in a 26 year old woman And Llewelyn Jones (2103), in a similar case, found both the lid signs, but on the left side only

Both lid signs, combined with absence of exophthalmia, were observed in one case each by Burton (752) in a 49 year old male patient, by Briner (1178) in a 21 year old woman, by W Rushton Parker (1896), by Roper (1911) in a 33 year old woman, by Low (1611) in a 23 year old woman, by Kast (Hunerfauth 1735) and by Kronlein (B Withmer 2034) in 4 cases In a 16 year old girl studied by Flatau (1963) only v Graefe's sign was "almost constantly" discernible, together with a goiter which had been present for 5 years and strong hyperhidrosis In a 56 year old woman patient of Berger's (2146), in whom the eyes did not protrude, v Graefe's sign was the only lid sign clearly developed In a similar case of Ball's (2453), a 24 year old girl, only the retraction of the upper lid was conspicuous Among 12 cases *assembled by Wilbrand and Saenger (2033)*, with no exophthalmia, both lid signs were clearly evident in one, in two a strong retraction of the upper lid was seen,

troublesome pulsations in the neck Palpitations, tachycardia, goiter and exophthalmia were entirely absent Pettesohn (1491) presented a 34 year old female patient who showed, besides all the lid signs only a marked acceleration of the pulse, tremor of the hands, and transitory flushing of the face A 39 year old worker, reported by Flatan (1936), showed a marked retraction of the upper lids and a pronounced *v. Graefe's sign* *In addition* he had a pulse rate of 100 to 120 per minute, sweated severely, showed tremor of the hands when they were held outstretched and at times he became *greatly excited He had felt* a weakness in the arms and limbs and often became frightened or was in a depressed mood He had been a poor sleeper for more than two years A goiter was not apparent In a 33 year old woman who exhibited no swelling of the neck or protrusion of the eyes, but who suffered from marked acceleration of the pulse, tremor of the hands, *a sense of heat*, tendency to sweating and weakness in the legs, Wilbrand and Saenger (2033) observed marked retraction of the right upper lid and lagging of *the lid in the lowering* of glance, but, on the other hand, there was a slight ptosis on the left side Cerised (Monthus 2952), in Lapersonne clinic, observed a 34 year old patient who, when first presented, showed only a striking retraction of the right upper lid Five months later von Graefe's sign also as well as a few other symptoms of Basedow's disease were discovered In one of the cases reported by Polack (3064), a 42 year old woman, considerable widening of the left lid aperture during lowering of glance had been noticed for two months as the only conspicuous disease sign A more thorough examination six weeks after the first one, showed moderate tachycardia, somewhat stronger pulsation of the carotids, rapid tremor, increased excitability, and *rapid loss of weight* A 37 year old woman came to Awerbach (2801) complaining of lachrymation and some lid swelling, both involving the right eye only A month later he found v *Graefe's sign, which, from* then on was continuously observable Other disease symptoms were absent Nothing is stated about the further course of this case Awerbach is of the opinion that he had before him an incompletely developed case of Basedow's disease

A few such cases, in which the lid symptoms of the disease were the signs noticed at first and also the most conspicuous ones, and where goiter and exophthalmia and cardiac palpitation were absent, I, myself, have had a chance to investigate and observe for a considerable time

A healthy-looking 27 year old woman, in whom an examination of the *internal* organs showed nothing pathological and in whom also hysterical stigmata were entirely lacking, presented herself at the polyclinic complaining of a feeling of tension in the left eye She herself saw in the mirror a gaping of the left lid *aperture* Actually, we found a conspicuous retraction and pronounced lag of the upper lid during lowering of plane of vision as well as infrequency of the involuntary *blinking* (see below §57), and a continuous tachycardia with 100-120 beats per minute No trace of a goiter or exophthalmia, or tremor was found Voluntary *closure of lids* took place promptly (In sleep the lid aperture was said to be incompletely closed) Upon gentle closure of the eyes a slight tremor of the lid could be noticed (*Rosenbach's* phenomenon, see below §104) Both pupils were equally wide and reacted promptly Nowhere within the range of the field of vision could double vision be discovered Under galvanic and dietetic treatment the marked gaping was gradually diminished and v *Graefe's* sign disappeared The tachycardia remained unchanged A pregnancy occurring in the meantime seemed to have no influence on the changes described

In a 53 year old woman with severe myopia we were struck by the great difference

§50. *As a rule in unilateral exophthalmia the lid signs also occur only unilaterally and, in fact, only on the side of the protrusion.*

Wilbrand and Saenger (2083) found both lid signs in the same eye in 4 cases of unilateral exophthalmia. Cases of exophthalmia on the right side only, with lid signs also developed only on the right are described by Roesner (310), Abadie (451), Hirschl (1208), P. Fridenberg-Jacobi (1308), Risley (1375), Miller (1755), A. Trousseau (2245), Terson (2242) in a 60 year old woman and a 48 year old man, Pribram (2727) in a young woman with an extremely severe case of Basedow's disease and Gifford (2666) in a 29 year old woman with only very slight exophthalmia. The wide gaping of the right lid aperture and the marked lag of the upper lid during the lowering of glance were the first abnormal symptoms in this case which caused the woman to consult a doctor, and at first they were much more conspicuous than after the symptom complex was fully developed.

Protrusion and lid signs of the left eye only were observed by Lang and Pringle (667), S. Snell (737), Barella (1171), Hitchman (1203), F. Fridenberg (1308), Pässler (1632) in 3 patients, Franke (2372), Guttmann (2380), and Stern (2411) in 1 case each. The latter found v. Graefe's sign clearly evident only when the right eye was closed.

§51. Lid signs, even more than the cardinal symptoms of Basedow's disease, are subject to conspicuous changes in regard to their occurrence as well as to the degree of their development. The wide opening of the lid aperture, for example, appears at first only during mental excitement or when the patients are *told to look* fixedly at some object. In many cases the lid symptoms occur only at intervals and at other times one or both of them are absent. We have already mentioned above that they may disappear and a change take place *in the* protrusion, and also that one of the two signs may regress while the other remains (§45 and §46). The lid signs, if prominent, may arise fully developed from the first. Later, when the symptom complex of Basedow's disease is fully developed they may seem much reduced.

In a case of acute Basedow's disease reported by Atkinson (2251), in which exophthalmia and lid signs were absent, a marked retraction of the upper lids occurred only 8 days before death, when psychosis in form of a mania had developed (see below §153). Kocher (2197) in one of his cases, could only identify v. Graefe's sign when the patient was in a reclining position.

§52. The fact that a study of the lid-signs made at various times during the course of the disease, may give a variety of results leads one to caution in judging the reports, sometimes widely divergent, concerning the occurrence and frequency of these important signs. This is especially true when using statistical data taken mainly from polyclinic case-history

and in three only v Graefe's sign was present Among similar cases Kocher (2197) observed both lid signs once, with gaping of the lid aperture 3 times, and the v. Graefe's sign alone once Among 89 cases in which notations were made about the lid symptoms by Murray (2213), a strong retraction of the upper lids is mentioned 9 times in cases where exophthalmia was absent, and once the incomplete correlation of the upper lid during lowering of the glance Among Kroug's (2700) 106 cases there were 18 with absence of exophthalmia and only v Graefe's lid sign Among the 46 cases collected by B. Donchin (2645) from the Breslau Medical Clinic, the lid signs were well developed in 1 case of those in which the exophthalmia was absent. In 1 among Garre's (Moses 2864) 24 cases, v Graefe's sign was the only eye symptom seen Among 52 cases reported by Landstrom (2849) there were 6 in which exophthalmia was not found and in one of these cases both of the lid signs were clearly present while in 2 the retraction of the upper lid was pronounced

Among 19 of my own cases in which no protrusion of the eyes was evident the lid signs appeared in 5, 3 times it was unilateral, appearing on the right side only, and once on the left In 1 case with wide gaping of the lid aperture, v Graefe's sign was only slightly indicated, in 3 it was only more or less plainly shown and once a retraction of the upper lid was very strong with a normal behavior of correlation during the lowering of the glance

§48. Several among the cases just described showed an absence of the lid signs on one side only

This was the case in one instance each as described by the following observers:—de Wecker, Snell, Wherry, Clarke, Gowers, Wilbrand and Saenger, Llewelyn Jones, Cerise, Polack and Auerbach, in 3 cases of my own and in 5 cases of Lang and Pringle

Cases have also been observed, however, in which, with bilateral exophthalmia, the lid signs could be observed only on one side

Friedrichson (763) reports such a case, a 28 year old woman with moderate protrusion of the eyes The left lid aperture was noticeably wider and the upper lid lagged behind the lowered glance Rummel (935) reports a 27 year old woman in whom only the right upper lid seemed strongly retracted, v Graefe's sign was clearly shown on the left On the left there was a slight ptosis In a case of Hunerfauth (1735), a 25 year old woman with moderate protrusion on both sides, v Graefe's sign was very pronounced on the left but absent on the right I, myself, in a 35 year old woman with moderate protrusion of eyes on both sides equally (18 mm beyond the orbital border) found the lid sign developed on the right side only, but very wide v. Graefe's sign was distinct only upon rather forcible lowering of glance

§49. On the contrary it may occur that in cases with unequally developed exophthalmia the lid signs are clearly shown in both eyes equally.

Volkel (945) tells of such a case, a 28 year old woman In the course of the disease, the left sided exophthalmia became somewhat reduced, while the moderately developed lid signs remained the same Above we have made mention of a case of Mooren, in which v Graefe's sign was distinctly evident in both eyes equally notwithstanding the fact that the bulb protruded on the left side only

upon the v. Graefe sign, found it lacking in 2 among 8 well-developed cases (2 sisters). Hill Griffith (658) found a wide gaping of the lid aperture 6 times among 10 cases in which attention was paid to this sign S West (686, p 79) considered "v. Graefe's sign as not very frequent" Brief notations about the lid signs are given in only 9 among his 38 cases In the other 29 cases they seem to have been given scant attention so that this author's reports appear to be statistically worthless. Ballet (747) is inclined to consider v Graefe's sign rather rare He was never able to recognize it in a fully developed form although he had seen a large number of Basedow's disease cases O Kahler (775) who had always given attention to the lid signs said that, according to his observations, von Graefe's sign is well developed only rarely—among 7 cases it was only mentioned twice—, while he declared that in Basedow's disease conspicuously wide spreading of the lid aperture, independent of the protrusion of the bulbs, is a very frequent, demonstrable sign

Lewis (777) noted v Graefe's sign 15 times among 22 carefully studied cases, that is, in 68% of them According to Eulenburg (825) v Graefe's sign is encountered much less frequently than is usually assumed Among 14 cases he found it in only 6 and in several of these it was not well developed Westedt (871) mentioned it 3 times among 6 cases, twice very distinct and once with a slight exophthalmia Rummel mentioned it (935) 7 times among 9 cases Cohen (1031) found v Graefe's sign 9 times among 16 cases from Mendel's Polyclinic, twice only weakly developed, and 4 times with a retraction of the upper lids Exophthalmia was always present though in several of these, also, it was only slight Among Mannheim's (1222) 42 cases from the same polyclinic both lid signs were more or less plainly evident in 16 cases, von Graefe's sign alone in 8, abnormal gaping of the lids in 4 cases In all, lid signs were found in 66 67% of his cases Maude, in 1892 (1056) made the observation that he had found the lid signs absent in his patients "fairly often" In 1897, on the other hand, he said "as a rule they are at least temporarily present" Of the two lid signs v Graefe's is the commoner From Ditisheim's summary it is seen that among 17 cases observed in the Zurich Medical Clinic, lid signs were present 11 times, von Graefe's sign was found distinctly developed only 3 times together with one case in which it was equivocal Pässler (1362) observed an unusually wide opening of the lid aperture in 20 among the 51 cases which were carefully studied, and of these it was unilateral in four Three times it was combined with left-sided exophthalmia (see above, §50) and only 9 times was von Graefe's sign well developed Hunerfurth (1735) among 18 cases from the Kastschen clinic noted von Graefe's sign 10 times and retraction of the upper lid only twice Thus there were lid signs in 12 cases or (66 67%) altogether According to F Kraus (1870) von Graefe's sign could be recognized in only about one third of all typical cases G Flateau (1963) found it only 16 times (in 53 33%) among 30 cases of Basedow's disease Among 12 cases of v Mikulicz's (2010) in which notations about the lid signs were made the findings were as follows the signs occurred together 5 times, von Graefe's sign alone 3 times, and the wide gaping of the lid aperture only once, altogether the lid signs were found in 75% of the cases Wilbrand and Saenger (2033) saw both lid signs distinctly developed in 28 among 39 cases, von Graefe's sign alone in 3, and only retraction of the upper lids in 2 cases, altogether lid signs were found in 84 6% of their cases Among 20 cases in the Hamburg Hospital collected by J Schulze (2118) exophthalmia occurred in all of them, both lid signs were present in 7 and von Graefe's sign alone in 8, altogether, lid signs were found in 75% of the cases. Among 9 cases from the Rostock Surgical clinic reported by Ehrich (1959) lid signs are mentioned 7 times Among 14 cases, J A Hirschl (2080) found both lid signs present 8 times, and in 2 cases a wide gaping

material Doubtless a retraction of the upper lids occurs more frequently than is mentioned in the publications of the case-history reports.

We often read about patients without any actual exophthalmia whose eyes looked large or had a disturbed look, an exaggerated stare, etc. This all points rather plainly to the Dalrymple sign, and with a pronounced exophthalmia this may be easily overlooked and the wide opening of the lid-aperture be attributed to the protrusion alone But I cannot agree with P J Mobius when he says (1478, p 25) that this sign is probably never absent, though naturally when it is weak it is easily overlooked. I have, myself, already given very careful attention to the lid signs. In a number of cases, even in those with pronounced exophthalmia which could be observed for a long time, I have failed to find either one or both of these signs Whether it was because the missing signs had been present at some other time, can, naturally, not be determined with certainty unless one has had the case under observation from beginning to end, a condition which is rarely fulfilled In regard to v Graefe's sign, Mobius, (1478, p 26) who considered it rather rare (1883), is of the opinion that it is the conclusion of some authors that these signs are definitely rare in Basedow's disease This is probably based on inadequate examination If every patient with Basedow's disease is tested properly and at various times, the signs, though not always found, will be discovered at one time or another This is certainly so in general but there is no question that, even with entirely professional examinations made at repeated intervals, the signs may be lacking in many cases.

From among numerous studies I shall select only a few in which with an especially pronounced exophthalmia the absence of the v Graefe sign or of both of the lid signs is expressly emphasized.

Thus, Baumler (203) mentions the absence of v Graefe's sign in a 49 year old man with unusually great exophthalmia v Graefe's sign was likewise absent, as stated by Fischer (465) in a 40 year old man, by Cross (653) in a 23 year old girl, and in a 27 year old woman, by Angel Money (674) in an 18 year old man, Schenck (938) in a 27 year old woman, Fr Muller (1134) in a 22 year old girl and a 36 year old woman who was under observation during the entire course of the disease It was also mentioned by Perregaux (1233) in a 19 year old youth and a 50 year old man, Bathurst (1268) in a 20 year old man, Hascovec (1318) in a 36 year old woman, W H Jessup (1455) in a 40 year old woman, Mattieson (1471) in a 22 year old servant girl, Owen (1490) in a 46 year old man, Steinlechner (1514) in a 20 year old woman patient, Donath (1840) in a 38 year old woman, and by H. Köster (1866) in a 50 year old woman.

Statistics have been given by a number of observers showing the frequency of the lid signs in their cases of Basedow's disease.

Among a large number of cases P Gros (591) found that von Graefe's sign was noticeably developed in only one Hughlings Jackson (663), who laid great stress

quency of the lid signs in Basedow's disease, we could well say that both, or one or the other would be encountered, at least temporarily, in something like two-thirds of all cases

§53. H. Gifford (2666) is impressed by the fact that in 3 out of 6 cases of Basedow's disease observed by him in the last six years the upper lid could be turned backward only with great difficulty and trouble, and that the connective tissue of the turned-back lid appeared almost completely bloodless. The exophthalmia was only slight in these 3 cases, v. Graefe's sign was already distinctly developed, and in 2 the Dalrymple sign was also present In one of these, that of a 29 year old woman with exophthalmia and lid signs, it was present only on the right side. The retraction of the upper lid was unusually marked, so that the lid aperture, during gentle closure of the lid, remained 2 to 3 mm wide and a horizontal fold remained stationary over the medial half of the tarsus.

In this case the patient had visited the doctor because it had struck her three months before, that "the right eye was larger than the left one Also it did not fully close during sleep, and when she looked downward it looked crooked" Gifford thought at that time that it was a matter of orbital swelling At any rate the other Basedow signs could not have been very conspicuous Later he learned that the woman, previously, before the first consultation, had suffered a great sorrow caused by the loss of a child, and since then had been very nervous and had had cardiac palpitation at times Five years later the mother of the patient noticed a slight swelling of her daughter's neck How long this had been there could not be determined When Gifford saw the patient again, 6 years after the first visit, he found a well developed goiter, a little larger on the right side than on the left, and a pulse rate of 110 beats (during rest it was slower) The right eye protruded now only slightly more than before, the right lid aperture was only a trace wider than the left, v Graefe's sign was evident, and the upper lid could not be turned back without difficulty

As a rule, Gifford had found difficulty in turning back the upper lid only in new cases In older, more developed cases, he had always failed to find this peculiarity That this difficulty in turning back the upper lid is not dependent upon exophthalmia is made clear from the fact that it was only slight in these particular cases Experience has shown that, even with marked protrusion of the eyes from any other cause, turning back of the upper *lid can be accomplished without difficulty* *Retraction of the* upper lid, taken by itself, is not sufficient to explain this sign. Probably, however, the lagging of the upper lid during lowering of glance is sufficient. If one desires to turn the lid back, one should have the patient look downward, whereby the lid extends itself over the bulbus and the lid fold disappears, then the lid can easily be turned back. But if lowering of the lid does not take place, or if, on turning the eye downward, a cramp-like re-

of the lid aperture, altogether lid signs occurred in 71 43% of his cases Among 23 cases collected by von Runge (2228) from the Gottingen clinic, von Graefe's sign was absent at the time of the exophthalmia and twice it was found with only slight protrusion, twice it was present only temporarily Thus it occurred in 81.8% of these cases Among 24 observations of Bruns (2268) von Graefe's sign appeared distinctly in only 10 cases, it occurred therefore, in only 41 67% of these. In 33 among 69 cases of Kocher's (2196) statements are given concerning the lid signs There was a more or less pronounced protrusion of the eyes in several, but in some, the lid signs were only equivocal In one case, with absence of exophthalmia, both could be demonstrated In 13 patients with protrusion of the eyes the mere presence of von Graefe's sign was mentioned In 7 of these the absence of Dalrymple's sign is expressly stated. Once v Graefe's sign is recorded with absence of exophthalmia In 3 patients with protrusion of the bulbi, and an equal number without it, an enormously wide gaping of the lids could be observed although v Graefe's sign was absent Thus lid signs were present in 78 26% of the cases The absence of both was mentioned in 10 patients with exophthalmia and in 5 without it G R Murray (2553) noted retraction of the upper lid in 70 among 125 cases and v Graefe's sign in 49 among 141 cases In 36 cases both lid signs were present together with exophthalmia, in 9 only v Graefe's sign, in 19 only retraction of the upper lids In 9 cases only the latter sign was present in the absence of protrusion, and in one v Graefe's sign was the only eye sign In 14 of the 22 cases about which v Mathes (2541) reports, the lid signs were present together with exophthalmia In 2 of these only v Graefe's sign was present and in 1 case only increased gaping of lid aperture and infrequency of blinking (see below §57) was noted In 2 cases the lid signs were present in the absence of exophthalmia; in 6 cases in which exophthalmia was missing the lid signs were also present Among Kroug's (2700) 106 cases v Graefe's sign was observed 43 times, 25 times combined with exophthalmia, 18 times without it, and 5 times only unilateral (in 40 56% of all cases) K Schultze (2749) reports that v Graefe's sign was evident in 15 among 50 cases of Riedel's It was always associated with exophthalmia and usually also with other eye signs He himself admitted, however, that these signs were, perhaps, sometimes overlooked or may not have been recorded in the case history reported. Among 54 out of 61 cases in which Frank Billings (2806) gave attention to the lid signs, v Graefe's sign could be detected in 45, in 4 among 8 men and 41 among 46 women (83 3% of his cases) R Stern (2991) came across v Graefe's sign in about three quarters of all well developed cases and in about one quarter of the incompletely developed forms (see below, §244) He seems to have found a wide gaping of lids more often

In 91 of my own cases, in which more exact descriptions of the lid signs have been recorded, both were more or less plainly evident in 39 cases, in 34 of these with exophthalmia and in 5 cases without it v Graefe's sign was present alone in 21 cases (3 times with absence of exophthalmia) and the Dalrymple sign alone 3 times (in 1 case without exophthalmia) In 28 cases the lid signs were absent and in 21 of these no exophthalmia was present Lid signs were evident in approximately 70% of my cases It must, however, be remembered that in a great majority of the cases the patients were subject to ambulatory treatment only and a few were actually observed only once

If we take into consideration only the results gained by reliable observers from a wide range of pathological material over a fairly extended observation period in order to draw a mathematical conclusion about the fre-

quency of the lid signs in Basedow's disease, we could well say that both, or one or the other would be encountered, at least temporarily, in something like two-thirds of all cases

§53. H Gifford (2666) is impressed by the fact that in 3 out of 6 cases of Basedow's disease observed by him in the last six years the upper lid could be turned backward only *with great difficulty and trouble, and that* the connective tissue of the turned-back lid appeared almost completely bloodless The exophthalmia was only slight in these 3 cases, v Graefe's sign was already distinctly developed, and in 2 the Dalrymple sign was also present In one of these, that of a 29 year old woman with exophthalmia and lid signs, it was present only on the right side The retraction of the upper lid was unusually marked, so that the lid aperture, during gentle closure of the lid, remained 2 to 3 mm wide and a horizontal fold remained stationary over the medial half of the tarsus

In this case the patient had visited the doctor because it had struck her three months before, that "the right eye was larger than the left one Also it did not fully close during sleep, and when she looked downward it looked crooked" Gifford thought at that time that it was a matter of orbital swelling At any rate the other Basedow signs could not have been very conspicuous Later he learned that the woman, previously, before the first consultation, had suffered a great sorrow caused by the loss of a child, and since then had been very nervous and had had cardiac palpitation at times Five years later the mother of the patient noticed a slight swelling of her daughter's neck How long this had been there could not be determined When Gifford saw the patient again, 6 years after the first visit, he found a well developed goiter, a little larger on the right side than on the left, and a pulse rate of 110 beats (during rest it was slower) The right eye protruded now only slightly more than before, the right lid aperture was only a trace wider than the left, v Graefe's sign was evident, and the upper lid could not be turned back without difficulty

As a rule, Gifford had found difficulty in turning back the upper lid only in new cases In older, more developed cases, he had always failed to find this peculiarity. That this difficulty in turning back the upper lid is not dependent upon exophthalmia is made clear from the fact that it was only slight in these particular cases Experience has shown that, even with marked protrusion of the eyes from any other cause, turning back of the upper lid can be accomplished without difficulty Retraction of the upper lid, taken by itself, is not sufficient to explain this sign Probably, however, the lagging of the upper lid during lowering of glance is sufficient If one desires to turn the lid back, one should have the patient look downward, whereby the lid extends itself over the bulbus and the lid fold disappears, then the lid can easily be turned back. But if lowering of the lid does not take place, or if, on turning the eye downward, a cramp-like re-

action of the upper lid occurs, as for example in the above mentioned case of *Ramsay's (see above, §44), then turning back the upper lid is unusually* difficult What makes the turning back of the upper lid difficult in this case is the presence of a rather thick swelling of the skin and subcutaneous tissue between the eyebrows and the upper tarsal margin. This was the condition in several of the cases belonging to this category (see below §211) That the conditions under discussion can disappear again in the course of the disease is confirmed by what has been said before I see no occasion to consider, as Gifford does, that this involuntary resistance to turning back of the upper lid is to be taken as a new sign of Basedow's disease Ch S Bull, in the discussion of Gifford's lecture at the New York Academy of Medicine, has reported that he had recently come across this condition in 3 cases, 2 with a slight exophthalmia and one with conspicuous exophthalmia. Strader, also, (2766) found this difficulty in turning back the upper lid as an early sign of Basedow's disease in a 21 year old woman She had definite exophthalmia and exhibited v Graefe's sign as well as a slight retraction of the upper lid These signs were much more developed in the right eye than in the left The pulse was 120, accompanied by a high degree of nervousness and exhaustion There was also a swelling of the skin of the upper lid, below the eyebrows, and heavy flow of tears Strader had this patient under treatment for several years before the ap*pearance of these signs, and had never noticed the least difficulty in turn*ing back the upper lid Since Gifford's report came to my attention, I myself, have tested all cases of Basedow's disease but could not discover this sign in any of them, not even in the newly developed cases.

§54. The question as to whether the lid signs so far discussed are characteristic or pathognomonic has been answered in various ways by different *authors. v Graefe (154) assigned* a pathognomonic significance *to* the sign which bears his name, especially in the developmental stages of the disease and in its milder forms, W. Bowman (513) holds it to be a very characteristic indication of the disease Several other authors did not hesitate to assign to it an important diagnostic significance for Basedow's disease. Seymour J. Sharkey (941), on the contrary, as well as G Flatau (1963) denied its importance as a valuable diagnostic sign If one must accept a sign as pathognomonic only when it is never or rarely absent in the disease concerned, and does not occur in other diseases, then we may not describe any of the signs of Basedow's disease as pathognomonic

We have just treated in detail the frequency of the two lid signs in this disease. Next, as to their occurrence under other conditions, it must be kept in mind that in many people a fixed stare at an object held in view is sufficient to cause great irritation of the lids. Now, if one has such persons

follow with their eyes while the object is being moved downward, then sometimes a distinct lagging of the upper lid can be observed. Many people are able to bring about this condition by simply staring. Sharkey, for example, observed this in a number of people and Flatau stated that he himself, as well as one of his assistants could reproduce this lagging of the upper lid at will, during the lowering of the glance, as could Albrand also (1086, p. 301). There are individuals in whom during only mildly excited conversation a marked retraction of the upper lids occurs, displaying a white margin above the cornea. This occurs to an even greater degree, as we shall see, under abnormal conditions of excitement (see below, §55). Seymour J. Sharkey (941), after observing a case in which v. Graefe's sign accompanied by tachycardia and cardiac palpitation was the only sign indicating Basedow's disease, was led to investigate further the question of whether v. Graefe's sign is ever found in healthy persons, or in those suffering from other diseases. For this purpose he had access to 613 patients who came to the clinic with various ailments. All, with one exception, were men between the ages of 33 and 78 years. He tested them for v Graefe's sign and obtained the surprising result that in 12, that is in nearly 2% of the cases, it was found to be well developed It seems to have occurred with few exceptions in patients with non-nervous ailments A few were suspected of having Basedow's disease (doubtful Graves' disease) Unfortunately Sharkey did *not* state the *number of these nor give any further* annotations. Of every 12 patients, 4 also showed a retraction of the upper lids Furthermore, he had observed in at least 24 others, among these 613 individuals, a lag of the upper lids on downward gaze This lag occurred when they were staring fixedly. He rightly called attention to the fact, mentioned above, that many people, when told to look at an object and follow it with their eyes, cannot stop staring, and then the lid signs are displayed unequivocally In many of these 24 cases of which he speaks he *succeeded in bringing these persons to a point where they did not stare*, but he believed that observers who look upon v. Graefe's sign as characteristic of Basedow's disease may, in doubtful cases, have added this to the list of signs of this disease. That may perhaps be correct I can only say, judging from my observations, that the experienced observer will usually be able to distinguish without difficulty the stare brought about by the lagging of the upper lids which I have had opportunity to observe often enough. This pseudo-v. Graefe sign is different from the phenomenon which A v. *Graefe has described The assumption is*, of course, that it is properly studied. For years I have especially observed this interesting sign and I can give assurances that I have never met with genuine lid signs unaccompanied by other extensive nervous symptoms or Basedow's disease

Impelled by Sharkey's surprising reports, Passler (1362) also tested

about 200 patients for v Graefe's sign. These patients came to the Jena clinic on account of a great variety of ailments Some were also patients of the surgical clinic there He found only one case where this sign was unquestionably present in an otherwise healthy person In this sturdily built, somewhat pale young man not only were none of the principal signs of Basedow's disease found or even suggested, but, also, every evidence of it was absent in regard to the nervous system v. Graefe's sign was displayed by him at different times and with greatly varying definitiveness

Hughlings Jackson (663) stated that he had once seen v Graefe's sign in a man without Basedow's disease Flatau (1963, p 112) mentioned only in general terms that he had twice found v. Graefe's sign in healthy persons who came into the clinic to accompany patients Likewise Wilbrand and Saenger (2033, p 44) stated that they had observed several cases in which, in entirely healthy individuals, v Graefe's sign was found more or less clearly developed Two cases of very pronounced retraction and little or no lag in the fall of the upper lids during downward turning of the eyes were observed by A Chevallereau and J. Chaillous (2273) in otherwise healthy persons

One of these was a 42 year old woman in whom, when she looked straight forward, a wide band of the sclera appeared above the cornea When the woman looked at her feet the upper lid remained absolutely motionless. Also, during voluntary closing of the lids, as well as in sleep, a small slit still remained open Complete closure of the lids required an effort The lower lid displayed entirely normal behavior There was not the slightest disturbance of the nervous system The only other matter worth mentioning was a loss of weight noticed by the patient herself for about half a year since the appearance of the retraction of the upper lids, and a loss of strength with a slight shortness of breath when climbing stairs Heart and lungs were quite normal This condition remained unchanged during the period under observation Perhaps this, however, represents an abortive case of Basedow's disease. In 2 cases there was a lid retraction on the left side only, and a disturbed correlation of the movement of the upper lids said to have been present since birth A 46 year old man came to the clinic of Quinze Vingts on account of a troublesome itching of the lids He was healthy in every other respect

Five years later Chaillous (2814) reported the similar case of a 62 year old woman She complained of an unpleasant feeling of dryness and tension in the eyes The upper lids were drawn back above the margins of the cornea and their free edges disappeared behind the somewhat swollen skin of the tarso-orbital folds On downward gaze the upper lids remained unmoved During sleep the eyes remained wide open Voluntary lid closure was incomplete and involuntary blinking occurred seldom In this case there was also a levator paralysis and an inadequacy of convergence, although laterally the eyes moved normally One must probably attribute to a supra-nuclear lesion both the accompanying paralysis and the spastic contractions of the levators of the lids The woman had never complained of double vision Other nervous symptoms were absent Visual acuity was normal after correction of the existing hypermetropia, and likewise the field of vision The patient was easily excited and stated that her hands trembled easily This rapid, delicate tremor in-

creased during the slightest emotion Otherwise no indications of Basedow's disease were present.

Trug (2777) reported to the French Ophthalmological Society another case which belongs here This 60 year old male suffered an influenza attack in December, 1904, and developed, in connection with this, neuralgic pains in the eyes which were slight and intermittent at first but later became frequent and almost continuous Subsequently, he could close the eyelids only with difficulty and finally not at all In *connection with this a sensation of dryness of the eyes developed* The pains still continued Otherwise, this robust man showed no disturbances of any sort The eye movements took place normally, being less easily executed only upwards The condition of the lids corresponded exactly with those in Chaillous case Fortunati (2492) saw a similar case of a 12 year old girl in whom tonic contraction of the lid

gaze the upper lid lagged or sometimes retracted still further Otherwise no disorders were evident The man came for a consultation because of a refraction error The retraction of the upper lid was unilateral also in a case described by G Mirto (2324), a 30 year old woman embroiderer who complained of having felt a painful tension in the right eye socket for about one year At the same time she had noticed that her expression seemed to be altered by the constant elevation of the right upper lid Actually the right lid aperture gaped about 18 mm while the left one was only 8 mm wide The lids could be closed The lid movement seemed to take place in normal manner (it was only a case of *le palpebre possono essere ammiccate*) No neurosympathic symptoms were present Suggestion had no effect A galvanic treatment brought about the disappearance of the abnormal signs after about 10 weeks

Two more cases belong here In each, the contraction of the lid levators took part in an abnormal associated movement during certain directions of glance and during convergence of the lines of vision One is reported by Browning (879) A 46 year old healthy man previously had been free of any disturbance of the ocular movements When he turned the eyes laterally the upper lid of the adducted eye rose somewhat higher, while that of the abducted eye sank During convergence on a near point, both upper lids were raised When the eyes followed an object moved from above downwards, the lids followed as far as the horizontal plane Upon further lowering of the eyes the lids stood motionless, and during the extreme lowering of the eyes they went slightly upward This might be a matter of a congenital anomaly

In a sturdy 27 year old man

servation was made that the upper lids just barely touched the upper part of the cornea when the glance was directed straight forward, while they rose somewhat more during the turning of the glance right or left If the glance was allowed to shift from the primary position slowly upward the eyes at first remained stationary The upper lid rose, revealing a wide band of the sclera Only then did the bulbus follow, and now the uppermost part of the cornea became covered Upon lowering the glance only the bulbus turned downward at first, while the upper lids remained stationary Only after it turned downward as far as possible, the lids were somewhat lowered, without, however, reaching the edge of the cornea As in the case of Browning, elevation of the lids was most easily accomplished during convergence of the lines of vision Even during fixation upon an object at a 30 mm distance, wavering in the position of the

upper lids began, so that they sometimes reached only to the edge of the cornea or remained somewhat above it

If the object of fixation was brought still nearer, the upper lid rose even more until, at a distance of 10 cm, a 3 mm wide band of sclera was visible above the cornea This became wider still if, while the object was kept at the same distance, it was moved downward The pupillary reaction was normal in every respect Aside from a moderate goiter, nothing abnormal could be discovered The pulse rate was 72 per minute In this case also we seem to have before us an abnormal association between the innervation of the lid levators and certain glance movements of the eyes.

From the findings presented above we believe we are justified in stating that genuine lid signs in otherwise healthy persons are found only quite exceptionally, and that Sharkey stands completely alone with his opposite supposition I cannot help taking his reports, as Passler also does, with the greatest skepticism Sharkey gives assurance that he took precautions against sources of error Still it seems plausible to me that, while he was successful in many of the 24 cases which he succeeded in preventing from staring, he failed in some of the 12 cases in which he believed he could demonstrate v. Graefe's sign without Basedow's disease signs or other nervous disorders

§55. On the other hand a number of reliable observations have established that the lid signs under discussion can be found well developed in various afflictions of the nervous system without the presence of any sign at all of Basedow's disease

I, myself, have observed such a case in a 35 year old woman with bilateral papilledema, a high degree of visual disturbance, severe headaches, vomiting, and other manifestations which justify the diagnosis of *tumor cerebri* v Graefe's sign occurred only on one side, but was clearly distinguishable Also Flatau (1963) found v Graefe's sign in a case of brain tumor

In a case of a patient with hysterical stigmata demonstrated by A Pick (1367) for the Verein deutsche Arzte, Prague, there was a pronounced retraction of both upper lids such, that with the glance directed forward, a several mm wide border of sclera remained uncovered above the cornea. On downward gaze the upper lid either did not follow at all or did so for only a short distance before retracting again Signs of Basedow's disease were entirely absent Flatau (1963) mentioned, without any further description, 2 cases of traumatic neurasthenia and hysteria and one of neurasthenia in which v Graefe's sign could be observed A Fuchs (2826) demonstrated in the Verein fur Psychiatrie und Neurologie in Vienna a case of severe accident neurosis in a man who exhibited v Graefe's sign without any other symptoms of Basedow's disease The manifestation seems not to have been present before the accident Also, Strasser (2887) saw such a case Together with other symptoms characteristic of traumatic neurosis v Graefe's sign occurred as a persisting condition No other indications of Basedow's disease were present Liebrecht (916, p 403) made the remark that he had often found both lid signs in a most distinct form in persons not afflicted with *exophthalmus Basedowii*, as for instance in persons with severe hysteria and those with other nervous eye signs An exceptional complication of a coal-miner's

nystagmus was observed by Smill (737) in a 37 year old miner a marked retraction and lag of the upper lids of both eyes upon lowering of the glance Basedow's disease signs were entirely absent (see also below §105)

F Raymond made the observation in the case of a patient with Thompson's disease that after a forceful closure of the lids the opening of the lids followed only slowly. If the patient looked downward the upper lid did not follow the eyeball at once In another subject suffering from the same disease he observed a retraction of the upper lids during violent bodily exercise The eyes protruded somewhat (see above, §43) and the glance became staring Flatau also mentioned a case of Thompson's disease with v Graefe's sign (1963, p 111) I, also, have observed v Graefe's sign in a 33 year old man with very pronounced Thompson's disease

In a 25 year old man who evidently suffered from myasthenic paralysis Goldflam observed a lag of the upper lids when the glance was directed downward

Fere (500) has seen in 3 epileptics a failure of movement or much hesitation of the upper lids when the glance was directed downward, and an infrequency of blinking Other signs of Basedow's disease were not in evidence

In a 29 year old man with unquestionable signs of a beginning tabes, Paesler (1362) observed v Graefe's sign In a 36 year old man who came to our clinic because of dizziness and double vision, and who, together with a right sided *abducens paresis*, displayed the unmistakable symptoms of tabes, I myself observed a wide gaping of the right lid aperture (4 mm wider than in the left, a 1 to 2 mm wide border of sclera uncovered above the cornea) On downward gaze, the right upper lid lagged noticeably, and during slow lid closure a marked lid tremor could be seen After 3 months the *abducens paresis* could no longer be detected but the lid signs were still evident

M. Köppen (1215) in Jolly's clinic observed v Graefe's sign in a patient with a complicated symptom complex A previously healthy 38 year old man developed a left-sided paralysis of the extremities, speech difficulty, twitching of the facial muscles (chiefly *orbicularis*), a continued nodding of the head with wider or narrower excursions, and rapid nystagmus with voluntary eye movements in all directions (a slight *strabismus divergens* with a high degree of myopia had been present previously) On downward gaze the upper lids remained stationary, but after a few seconds they followed the eyeball If the gaze remained downward for some time, the upper lids showed a definite tendency to retract The paralysis improved at first Repeated attacks, an increasing dementia, and death followed 2 years after the first attack Extensive changes in the cerebral cortex resembled, under microscopical examination, those of *dementia paralytica* There were extensive arteriosclerotic changes in the walls of the blood vessels Vessels with especially marked changes were found in the region of the oculomotor nucleus No changes were found in the ganglion cells of this nucleus

A lag of the upper lid during downward glance was observed by Koppen in several other patients with nervous ailments, although none with neurological involvement as extensive as in the case outlined above Sometimes it was observed in patients who were in a state of excitement A 30 year old woman patient had an organic hemiparesis Following a fright she was in a state of great excitement Mobius (1024) observed a wide gaping of lid apertures and v Graefe's sign as in Basedow's disease Savage (586) states that he has often observed exophthalmus accompanying mania Acceleration of the pulse and slight swelling of the neck served as the first sign of the attack Jung (388) claims to have seen protruding eyes in several cases of mania in factory workers, each time acting as precursor of the reappearance of an attack These observations probably concerned only a conspicuous retraction of the upper

lids In such cases the sign is always transitory and often cannot be found shortly afterward

In a restaurant owner who suddenly developed a toxico-traumatic, *radialis* paralysis on the right side, Flatau (1963) observed conspicuously wide lid apertures and a distinct v Graefe's sign A musician of 55, who had been alcoholic for years, and had, at the same time, eaten insufficiently, displayed a strong retraction of the upper lids and a v Graefe's sign which could be seen at all times in its complete manifestation Also he had a goiter which had been present from youth and which Flatau believed attributable to alcoholism

Among the other afflictions of the nervous system in which Flatau found v Graefe's sign he cites one case each of bulbar paralysis, *diplegia spastica cerebralis*, and apoplexy

Oppenheim (2417, p 1320) once found a unilateral v Graefe's sign in a case of *paralysis agitans in which the tremor was also confined to one side*

A case which is interesting in many ways and which Michel (2322) has published under the title of a unilateral hereditary and congenital disturbance of the innervation of the cervical sympathicus must also be discussed here A 9 year old boy showed an ususual widening of the right eyelid dating from shortly after birth Actually this was because of a marked retraction of the upper lid Upon looking downward the corresponding movement of the upper lid did not take place During sleep the lid aperture could not be closed The right eyeball protruded slightly The right side of the face appeared redder than the left and felt warmer to the touch There was no change in the sweat secretion Both pupils were equally wide and reacted in the normal way The visual function of both eyes were normal The right eyelid was placed somewhat deep and could not easily be turned upward

The explanation of the above symptom complex as a unilateral disturbance of the cervical *sympathicus* with accompanying stimulation and paralysis of certain fibres can most certainly not, in my opinion, stand up under objective criticism This case does not show the change in the diameter of pupils which is so characteristic and practically never absent with innervation disturbances of the cervical *sympathicus* Furthermore, the tone of the lid muscles was affected only in the case of the upper lid, while the lower one did not seem more shifted in position than would have been expected from what was said above (§43) Finally the retraction of the upper lid was very much stronger than stimulation of the organic lid levators could ever have produced Also the accompanying movement of the upper lid in looking downward is by no means inhibited by a stimulation of the *sympathicus* One need only call to mind the relationships in the pattern of a paralysis of the oculo-pupillary fibres of the *sympathicus* Aside from the miosis, which was never absent, the ptosis was still only slight and the lower lid seemed also somewhat elevated That leaves then only the more pronounced flushing, greater warmth, and increased turgescence of the right side of the face, all of which are to be attributed to a paralysis of the vaso-motor fibres The slight protrusion of the right eye is sufficiently explained by an unusual retraction of the upper lid Nothing is stated concerning the pulse rate which, even with the assumption of an innervation disturbance in the *sympathicus*, should not be left entirely out of consideration In view of the definitely determined paralysis of the levator of the right eye it is probably more accurate to place the focus of irritation in the area of the nucleus of the *levator palpebrae super* The nature of this perpetual condition of irritation remains, however, unclear (see also above, §54, Chaillous' 2nd case)

In the Greifswald Medical Society, Mosler (924) demonstrated the case of a 57

year old man in whom a right sided moderate exophthalmus, a slight ptosis of the right upper lid, and v. Graefe's sign were evident on the same side. A hard, non pulsating tumor the size of a child's fist in the right lobe of the thyroid had pushed the larynx far to the left and caused breathing and swallowing difficulties. The enlargement had first been noticed about four weeks before and had reached most of its ultimate size in five days. Mosler had pronounced it a scirrhus tumor of the thyroid gland and advised extirpation as soon as possible. Concerning the further course no information is given.

§56. In view of the diagnostic value of the lid signs, it seems desirable to call attention to a few of the more unusual causes of an abnormally wide lid aperture and of a retarded accompanying movement of the upper lid on downward gaze since these seem to be less well known.

One encounters these signs especially in cases of muscular palsy. One form, which can occur only unilaterally, is most plainly apparent in unilateral *ophthalmoplegia exterior* with ptosis of moderate degree, or in unilateral oculomotor paresis. Another is unilateral levator paralysis with accompanying ptosis, a paresis of the *rectus sup.* and of *obliquus inf.* of one eye, if the paralysis affects the eye with the better sight, which would be used alone in a fixation gaze. In this case the weaker or amblyopic eye need by no means show a marked deviation. Under such abnormal conditions exceptionally powerful innervation of the weakened levator is *required to* keep the line of vision horizontal. A corresponding elevation of the paretic upper lid takes place as a *result of the associated innervation of the levator palpebrae sup.*, by means of which the pupil is uncovered to a sufficient degree. This increased innervation for fixation of the eye makes itself felt in a correspondingly strong secondary upward shift *of the nonparalyzed* eye. In paresis of the *rectus medialis* this movement is upward and outward with powerful elevation of the upper lid. If the focusing eye follows a moving object slowly downward, the difference in the width of the lid apertures remains and is especially conspicuous at the beginning of the downward movement. I have had occasion to observe and analyze cases of this sort several times.

A conspicuously wide gape of the lid aperture is also evident at times in a bilateral associated paresis of the levator of the eyeball. Other associated eye movements may be more or less weakened. In a resting position the lines of vision are somewhat lowered. If an object in the horizontal plane is brought into focus either a more or less energetic backward turn of the *head is necessary, or, in case the* levator needs a still greater stimulus, a very powerful nervous impulse to these muscles occurs. As a result of association of elevation of the lid with elevation of the plane of vision this increased innervating stimulus which affects the levators of the bulb results very strikingly in the abnormally strong action of the *unweakened levators palpebrae sup.* A disturbance of the accompanying movement of the upper

lid on downward gaze comparable to v. Graefe's sign does not appear here for understandable reasons.

In one of our cases, that of a 29 year old man, the lateral movements and convergence were intact, the depressors were slightly weakened, and the levators very much so First the right pupil, then the left one, was somewhat wide, both reacted slowly to light, but promptly to convergence. The visual acuity and eye grounds were normal Furthermore a loss of memory and ability to reckon, and a weakness of the orbicularis oris branch of the right facialis were observed Perhaps this indicated early symptoms of a *dementia paralytica*

In the 2nd case, that of a 48 year old man, all associated eye movements were weakened and also, to a slight degree, the convergence The bulb levator however seemed to be by far the most affected Pupil reactions were normal A wide gape of the lid aperture had been noticed by the patient for a long time Combined system disease may have been indicated here Under special circumstances an abnormal gape of the lid aperture can appear with bilateral levator paresis as shown by an observation on a 38 year old woman in whom the paralysis of certain eye muscles of both eyes in changing combination was demonstrable There was no disturbance of the nervous system and no sign of myasthenia or of hysteria There was a reduction in the lateral deviation toward both sides, with excessive participation of the *rectus lateralis* On downward gaze the left eye lagged somewhat, as in a paralysis of the *rectus inferior* Elevation of the line of vision was limited on both sides, particularly the right On forward gaze the right upper lid was drawn so far back over the margin of the cornea that a band of sclera about 2 mm wide became visible

With complete paralysis of the levators of the eye, a wide gape of the lid aperture may occur when an attempt is made to look upward The eyes in this case sometimes show mystagmus-like lateral or rolling movements.

Such was noted in a case of Kahler's and in one of Wilbrand and Saenger (2033, page 41), both following attacks resembling apoplexy in men in their early thirties.

Often one observes, in cases of unilateral more or less complete oculomotor paralysis with beginning recovery that, during the effort to look downward, a relative lag corresponding to a retraction of the paretic upper lid occurs This lag results in a conspicuous gape of the lid aperture. This manifestation has a close similarity to v Graefe's sign in Basedow's disease and may, following Koppen's (1215) example, be described as the pseudo-Graefe's sign In the majority of the cases of this group a distinct elevation of the upper lid follows the order to look downward when the paretic eye is in the horizontal line of vision or converging on an object placed in the medial plane In a number of cases a more forced depression of the upper lid occurs during abduction The lag or retraction of the upper lid is most noticeable during lowering of the plane of vision, but sometimes occurs only when the paralyzed eye is called upon for adduction, that is, convergence. During bilateral lowering and abduction either both upper lids seem equally elevated or that of the paralyzed side remains lower. A few

observers do not seem to have paid much attention to this behavior. It is, however, by no means impossible that this difference between adduction and abduction was, nevertheless, present. It is in only 1 case expressly pointed out that no such difference occurred during the lowering of the glance.

The phenomenon usually appears first at a time when the ptosis is only very slight. Of the eye movements, chiefly the lowering and adduction, or only the former, are affected. In all cases it becomes evident only when the weakened muscles are called into action by a powerful voluntary impulse

In this connection let us remember those most peculiar cases in which a unilateral paralysis of the *oculomotorius* is congenital or acquired in childhood Elevation of the paralyzed upper lid is without voluntary control and occurs in rhythmic, rather regular intervals Simultaneously with adduction, a narrowing of the pupil, and an accommodation cramp occurs The few cases, up to now not well known, are reported by von Rampoldi, Fuchs (1103, p 19), and Axenfeld and Schurenberg An analogous case was described by Bielschowsky, only, here the automatic movements of the paralyzed upper lid were absent

The peculiarities described above, especially the change in the position of the upper lids on downward gaze with simultaneous adduction or abduction, provide an essential criterion for distinguishing the pseudo-Graefe's sign from Basedow's disease, where, as we have seen, it also occasionally occurs unilaterally and without exophthalmia

This pseudo-Graefe's sign is to be understood as a kind of associated action which takes place with an incomplete or unequal paralysis of the *oculomotorius*. The motor impulse, directed to the paralyzed muscle, spreads out into the less damaged innervation channels It is noteworthy that none of the cases belonging in this category involves a congenital disturbance although the symptom may sometimes actually appear very early. It is also noteworthy that in none of them could an exclusively nuclear lesion be assumed with any probability

Cases of associated movement or expansion of innervation into nearby functional nerve channels more responsive to an impulse are recorded in the clinical literature in no small number We have already referred briefly to a few of these We can go further into detail only concerning those in which a phenomenon comparable to v Graefe's sign appears.

Among the cases described by E Fuchs (1103) as involving an association of the lid movement with lateral deviation of the eye there is one which belongs here In a 41 year old man with unmistakable signs of tabes there was a paresis of all the external muscles of the left side innervated by the *oculomotorius* The upper lid extended somewhat downward over the upper edge of the pupil During fixation with both eyes on an object placed in the median plane, there followed, simultaneously with medial shift of the left eye, which had been turned outward, a marked elevation of the paralyzed upper lid This paralyzed lid became higher than the healthy one

If the patient was told to follow an object with both eyes while it was being moved downwards, the left upper lid did not follow the order As the glance continued downward a wide band of sclera remained uncovered above the cornea while in the right eye the lid reached almost to the pupil (p 14)

Brixa (1514) has described a similar case. In a 33 year old woman, there had developed about a year previously a paresis of all the muscles of the right eye which were innervated by the *oculomotorius* The cause could not be determined During vigorous adduction the lowered upper lid rose so much that a 1 5 mm wide band of sclera was visible above the cornea, during abduction the lid sank considerably When the glance turned downward, the upper lid remained stationary At the limit of downward gaze the upper lid did not reach the margin of the cornea

In a 33 year old woman patient of Kraft-Ebbing, reported by Droogleever Fortuyn (1841), a left sided ophthalmoplegia exterior and interior was discovered among the signs of a *polioencephalitis superior acuta* At the time of observation, about half a year after the occurrence of the paralysis, the various nerves seemed to be affected to a very unequal degree While the pupils and accomodation were almost completely paralyzed, the adduction and abduction were only slightly impeded, especially the latter Raising and lowering were reduced to a minimum and the rectus innervation seemed to be affected to a greater degree than that of the obliques Ptosis was still present only to a slight degree Opening of the closed lids was accomplished more slowly on the left than on the right On turning the bulbi to the right, the upper lid retracted slightly With maximal adduction of the left eye both apertures appeared equally wide On turning to the left the left upper lid moved distinctly farther downward On looking downward, the left upper lid rose to a height, otherwise never seen, such that a 2–3 mm wide rim of sclera became visible above the corneal border The gape of the lid apertures was greatest during simultaneous lowering and turning to the right Only the right eye actually executed this movement

Wilbrand and Saenger (2033, p 57) tell of a 46 year old woman in whom a total left-sided *oculomotorius* and *trochlearis* paralysis appeared suddenly, probably from a specific cause After inunction treatment and iodide therapy, a noticeable improvement of the muscular paralysis occurred With the glance directed straight forward, the position of the eyes and lids appeared nearly normal. Only on downward gaze could a limitation of motion be determined They observed that during extreme lowering of glance, such an elevation of the upper lid took place that a broad band of sclera was uncovered between the lid and the margin of the cornea

W Hinkel had the opportunity to observe 6 similar cases, 3 at the Rostock eye clinic and 3 in Zittau A 24 year old woman was recovering from a sudden complete *oculomotorius* paralysis of the left side When ptosis had almost entirely disappeared and only the bulbus movements downward and inward were still limited to a considerable degree, a surprising sign could be observed While the object of fixation was being moved downward and toward the median plane the left upper lid began to move upward unexpectedly and assumed a considerably higher position With the glance directed straight downward, both lids turned downward in the usual way Regardless of the improvement in the paralysis, the manifestation continued quite definitely during the whole period of observation

The second case was a 70 year old woman suffering from pronounced arteriosclerosis She had developed a total right-sided *oculomotorius* paralysis With improvement of the ptosis occurred an elevation of the right upper lid when the eyes turned left. In this movement the paralyzed lid reached the middle of the lid aperture On turning to the right, a distinct depression of the right upper lid occurred With

fixation on an object below and in the median plane came such a strong retraction *of the upper lid that its free edge stood 4 mm higher than that of the left one*, which was lowered normally. On outward and downward gaze both lids followed the movement of the bulbus equally.

The third case was a 4 year old boy with a ptosis and paresis of the branches of the *oculomotorius* controlling the eye muscles left after removal of a retrobulbar echinococcus cyst from the right orbit. The resection had been done by a Kronlein osteoplastic operation In this instance the same symptoms as in the first two cases appeared at the time that the ptosis began to diminish

In a 10 year old girl a paralysis of all the muscles of the left eye innervated by the *oculomotorius* was discovered This had probably been the result of an injury during her delivery by means of instruments Upward movement was almost completely inhibited, and downward movement extremely limited The left eye executed only very slight rotary movements At the time of the observation ptosis was only slight When the patient looked downward a marked retraction of the left upper lid took place This retraction was still greater when the eyes turned downward and at the *same time to the right A band of sclera several mm wide became visible above the* cornea

In the case of a 36 year old man developing tabes a definite elevation of the right upper lid occurred with downward gaze during progressive improvement of a right *oculomotorius* paralysis When the ptosis had nearly disappeared, downward movement of the eye still was quite limited

In the final, rather incompletely described case, concerning a 46 year old woman, there was a slight paresis of the left *oculomotorius* Only the action of the depressor seemed to have been almost entirely inhibited When the patient was told to look downward, the left upper lid rose Its free margin came to rest about 2 mm higher than that of the right Simultaneous adduction or abduction had no influence upon the width of the lid aperture.

Lindenmeyer (2407) tells of a similar case at the University Eye Clinic in Giessen A woman of 62 had a paresis of the right *oculomotorius* The various branches were affected unequally While the ptosis was very slight and the adduction only slightly limited, the movements upward and downward seemed inhibited to a high degree On the leftward movement of the right eye a slight elevation occurred, and on movement to the right a definite lowering of the upper lid took place

On downward gaze the right upper lid started to carry out the movement with it, only to linger in this position as the object of fixation was moved further down, or to retract so far upward that it reached the upper corneal margin of the eye This occurred when the eye was turned only slightly downward

Blaschek (2463) has also reported 21 such cases from the Graz Eye Clinic In a 26 year old woman the observation was made during the recovery from a left-sided *oculomotorius* paralysis During downward gaze the left upper lid remained 2 to 3 mm lower than the right while the lower lid sank a little, in the usual way, so that finally the left lid aperture gaped 7 mm wide as compared to an aperture of 4 or 5 mm in the normal eye The left eyeball executed only a slight lowering movement with a distinct roll resulting from the action of the intact *obliquus superior*. With extreme shift to the right the lid aperture widened somewhat With an energetic turn to the left it became somewhat narrower A 26 year old woman patient had suffered a syphilitic infection During the recession of the right-sided *oculomotorius* paralysis she displayed exactly the same signs. The explanation which Blaschek gives for the failure of the upper lid to fall on downward gaze is based on such unphysiological grounds that it requires no further consideration

A similar case has recently been demonstrated at the Medical Society in Marburg by Krusius (2847) The patient was a 32 year old woman with a right-sided ophthalmoplegia The paralysis had been complete, but was then in a stage of recovery Since there was also a right-sided optic atrophy and a disturbance in the region of N *frontalis, supra,* and *infratrochlearis,* the process involved retraction of the right upper lid but in such a way that no differences in the width of the two lid apertures

I myself have had opportunity to observe several cases which belong in this group I should like to report here in more detail on 3 typical of these. A 39 year old woman fell from a wagon and suffered a skull fracture with a right-sided facial paralysis and a total *oculomotorius* paralysis A half year later the facial paralysis had disappeared and that of the *oculomotorius* had so greatly improved that with forward gaze only a barely perceptible depression of the right upper lid could be distinguished. Adduction and lowering seemed to be limited to only a slight degree

of sclera lay uncovered above the upper margin of the cornea Upward gaze was still very strongly inhibited in this case The right upper lid went up moderately The right pupil was distinctly wider than the left and fixed, but it contracted during convergence and upon voluntary closure of the lids

The second case was a 31 year old woman who, about a year before, had suddenly fallen ill with violent headaches and double vision Somewhat later the left upper lid had fallen When she came to us there was distinct ptosis With downward gaze the left upper lid fell only slightly without following the eyeball The sclera above the cornea was uncovered, showing a 2 mm wide band, and the left aperture opened wider than the right one in the primary position This movement was followed by a distinct inward rolling of the bulb resembling a *trochlearis* action Elevation of the left eye was still greatly impeded The adduction seemed not to have been much impeded, but during convergence the left eye lagged distinctly Visual acuity and accommodation were normal, and likewise the pupils There was no basis for assuming that this was a cured syphilitic infection

The third case was a 28 year old woman who, 12 days before she first came in, had been troubled by violent headaches on the right side associated with fainting and vomiting When the headaches diminished after a period of eight days, double vision began and soon afterward there was a droop of the right upper lid We found, along with normal refraction and visual acuity, an almost complete *oculomotorius* paralysis of the right eye The paralysis increased at first and became complete Three and a half months after the onset a definite improvement had occurred, and at the same time a retraction of the right upper lid developed The right palpebral fissure appeared wider than the left On downward gaze the right upper lid remained unmoved On upward gaze it went somewhat further upward Closure of the lids could be accomplished equally well on both sides When the patient turned the lowered

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motorius, and convergence was executed relatively well The pupil opened for distant vision to a diameter of about 7 mm and was completely fixed, but showed good reaction to convergence and a definite lid closure reaction

Finally a case described by W Albrand (1086) as Basedow's disease seems to me to belong here. The woman, 45 years old at that time, had been infected with syphilis by her husband twelve years before She complained of twitching in the right upper lid and occasional double vision when looking downward During the lowering of the gaze the right upper lid sometimes followed the eyeball in normal fashion, but it lagged about 2 mm behind the left, and then immediately retracted again at the end of the movement Use of colored glasses temporarily demonstrated crossed double images during downward gaze These, in Albrand's opinion, would indicate a slight right-sided paralysis of the *rectus inferior* It greatly disturbed the patient by distortion of orientation during downward gaze The description of the double images is so inadequate that a definite diagnosis of the paralysis cannot be made But this much is certain: it must have been a paresis of one or both depressors of the right eye During reaction to light the right pupil remained a little wider than the left The proximal point of focus for the right eye was 3 cm beyond that for the left. After treatment with iodide of potassium the patient ceased to be troubled by twitching of the lids. The diplopia disappeared and the difference in the proximal focal points disappeared This woman then felt that she was entirely well However, there gradually developed an abnormally wide gape of the right lid aperture with forward gaze A lag of the upper lid upon lowering the gaze could now be observed constantly Albrand himself admits that the paresis of the *pars palpebralis* of *musc orbicularis*, simultaneously existing and later plainly becoming evident, was not enough to account for the manifestation No plausible ground is given for the assumption of Basedow's disease, although six months before the appearance of the lid twitch and double vision this patient had suffered for fourteen days from tremor and cardiac palpitation following emotional excitement

The foregoing descriptions make it evident that caution is needed in the formation of a critical judgment about an existing retraction and failure of associated movement of the upper lids during downward gaze in doubtful cases when eye-muscle paresis conditions are present simultaneously

§57. The third lid sign, as already indicated above, consists of the infrequency and incompleteness of involuntary blinking. It was studied in detail in 1869 by C Stellwag Von Carion (235) and will be designated as the v. Stellwag's sign The discoverer concluded from his experience that it could be counted among the most constant of the eye signs in Basedow's disease Indeed it is the most characteristic sign from the very beginning of the eye involvement and during the entire subsequent course of the basic processes in all cases except those in which there are other indications of a subsiding neurological disorder After v Stellwag's attention was directed to it he was able to distinguish this sign very clearly. He believed, certainly not mistakenly, that this phenomenon played no small part in the staring, hard expression which is so striking in the physiognomy of these patients Normal persons execute three, five, or even ten lid movements per minute at quite irregular intervals. Patients with Basedow's disease sometimes go several minutes before even a slight twitching of the lid margins is perceptible As already mentioned above (§43) voluntary

lid closure in Basedow's disease takes place, as a rule, quite unhindered. After one closure several more extensive lid movements follow, at times, in rapid tempo one after another. Afterwards, the interval again lengthens, and the lowering of the upper-lid margin becomes as incomplete as before.

In many cases described in pertinent literature this sign, it seems, has not been given due attention. One may not conclude at once, from the infrequency of its mention, that it is often absent According to my experience, and that of other observers who have paid attention to this sign, it is nevertheless much less frequent in occurrence than the two other lid signs. When it is present, it usually makes itself evident in combination with the others

When Naumann (44) stated that in his case the lids formed a narrow border above the greatly protruding eyes and that their movement was entirely inhibited, he probably had before him the sign in question combined with a strong retraction

O Kahler (775a) noted the infrequency of involuntary lid movement only 3 times among 7 cases, but he declared that the sign (775a) was found often. Ditisheim (1293) mentioned it only once among his 17 cases Among Hungerfauth's (1735) 18 cases the sign is noted only 5 times In 58 among Kocher's (2197) numerous cases statements are found concerning v Stellwag's sign, 31 times it was present, that is, in 53 45%, twice with absence of exophthalmia In the rest of the 27 cases its absence is expressly mentioned In 13 of these latter the other lid signs were also absent, 6 times they were combined with protrusion of the eyes. Bruns (2268) observed infrequent blinking "very rarely" among his 24 cases Infrequency and incompleteness of blinking is expressly stated only in 11 of my own cases One or both of the other lid signs were always present When they were absent, v. Stellwag's sign was also absent It was frequently absent when the other lid signs were clearly developed In a number of cases, to be sure, not enough attention was given to the frequency of the involuntary blinking Also, several other observers emphasized especially that with definite retraction and disturbed associative movement of the upper lid, infrequency and incompleteness of the lid motion could not be discovered. This was found by Lang and Pringle (667) in their 6 cases, likewise in Steiner's (513) case of a 9 year old girl showing a conspicuous gape of the lid apertures with only moderate exophthalmia and absence of v Graefe's sign The lid closure occurred here 5 to 7 times a minute; the upper lid, however, did not come fully into contact with the lower one. It is only in exceptional cases that v Stellwag's sign is the only one of the lid signs present This happened in 1 case of Perregaux (1233), a 19 year old girl, who, at the same time, exhibited pronounced signs of hysteria and strong exophthalmia The other lid signs were lacking, while involuntary blinking occurred rarely and incompletely

It has also been found that at different times v. Stellwag's sign is not always equally well developed With the regression of the other lid signs blinking usually becomes more frequent and more complete. Probably it is only in exceptional cases that infrequency and incompleteness of involuntary blinking is found without Basedow's disease symptoms, especially in hysteria In many instances such patients are observed to blink abnormally often. We shall return to this matter again further on

§58. Although we have seen that the lid signs are, to a certain degree, independent of one another in their occurrence, yet they can well be traced back to a common cause. Attempts have been made to explain them in various ways: 1. by a constant increase in the state of contraction of the smooth lid muscle innervated by the *sympathicus*, H Muller's *musc. palpebralis superior* and *inferior;* 2. by a decreased tension in the *orbicularis* muscle of the lid, 3. by the lesion of an assumed coordinating center for the action of the levator and the *orbicularis* on the one hand and the levator and depressor of the eyeball on the other hand, 4 by an increased tonus in the levator *palpebrae superioris*, and finally 5 by mechanically acting forces resulting from anatomical relationships Evidence has been set forth in detail that an attempted explanation based on exophthalmia is unreliable. (See above §13, §16, §17, §18, §57). We have only to add the definite assurance that when there is a protrusion of the eyes due to other causes no lid signs are to be found ever which would correspond to the signs in question, although the lid movements seem, often enough, to be disturbed in such cases.

§59. The dependence of the lid signs on an increased tonus of the smooth lid muscles discovered by H. Muller, has been pointed out by A v Graefe in 1864 as "probable to a certain degree" This interpretation stands well with the *sympathicus* theory of Basedow's disease which was in vogue at that time and which had its supporters until very recently: (Jessop 666, Gowers 1012, A. Furst 1309, Abadie 1684 and others, e g, V Michel in his *Handbuch*, First Edition, Vol. IV, Part 2, p 417, O Schwarz, Die Funktionsprufung des Auges, 1904, p. 296, Landstrom 2849 and others) A few authors even speak of a tonic cramp, a spasm of the Muller's muscle The increased gape of the palpebral fissure resulting from strong cocaine or adrenalin action, which is known to be traceable to stimulation of sympathetic nerve endings, has been considered analogous to the lid signs in Basedow's disease (W. Jessop 666, W. Edmunds 1299 and others). Indeed Jessop stated that the lag of the upper lid upon lowering of the plane of vision is also often definitely conspicuous In one case of Basedow's disease with bilateral exophthalmia and well-developed lid signs he dropped a 2% cocaine solution twice into the left eye. After 20 minutes the left lid aperture was wider than the right and a wide band of sclera appeared uncovered. Jessop was then convinced that a stimulation of the peripheral endings was added to the central stimulation of the *symphaticus* which apparently was the cause of the lid signs in Basedow's disease. Much more probable, it seems to me, and more in accordance with the facts, is the opposite line of reasoning, namely, that a stimulation of the sympathetic fibers plays no part in producing the lid signs, but that the increased gape of the lid aperture due to the cocaine action was in addition to an already

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sign is clearly developed, a disturbance can in no way be demonstrated, as we shall see later (see §84 below).

S. Sharkey (941, p 210) considers v. Stellwag's explanation of the lid signs to be the most satisfactory. A. Maude (1056 and 1620) even spoke of a paresis of the *orbicularis*, as a result of which a purely relative predominance of the muscles which open the lid aperture would occur That it cannot be a question of paresis has been expressly emphasized by v Stellwag. The lower lid lies smoothly against the bulbus and its free edge stands no lower. Also it is known that in facial paresis nothing similar to the lid signs in Basedow's disease can be observed.

§61. I supposed formerly (181, p 996) that in order to explain v Graefe's sign it was necessary to assume a lesion of a coordination center by which the consensual action of the levator and *orbicularis* on the one hand, and the levator and depressor of the eyeball, on the other hand, is controlled. I have attributed the abnormally wide gape of the palpebral fissure as well as the infrequency of involuntary blinking to a disturbance in the reflex centers from which the radiating impulses from the retina and from the sensory nerves of conjunctiva and cornea to the motor apparatus of the lids are controlled. I have since given up this conception not only because all anatomic evidence for the postulated coordination center is lacking, but also because as we shall see below, such an assumption is not needed for a satisfactory explanation

W. A Fitzgerald (541) has accepted my view fully and completely Also J. Hutchinson (664, p 34) seems to acknowledge a similar view when he considers v Graefe's sign as consisting of a disturbance of the association between the sensory and motor nerves of the eyeball and the orbit In fact he even suggests that two kinds of fibers might exist, one for the association or reflex movements, and the other for the voluntary ones Though A Eulenburg in 1873 (283, p 48) saw in v Graefe's sign a manifestation which indicated an involvement of the *sympathicus* he expressed himself in 1889 (825) as against the dependence upon a functional disturbance of the smooth lid muscles, and held himself in agreement with my explanation of a lesion in the central mechanism of motor association between the upper lid and the muscles which turn the eyeball around its horizontal axis R Hitschmann (1209) also expressed himself as of my opinion, and suggested that continuing or transitory changes in the state of contraction of the arteries supplying the corresponding centers play a part.

§62. Even the first observers of the abnormally wide gape of the palpebral fissure, Dalrymple and Wh Cooper, introduced into their descriptions the impression which the manifestation made upon them without

existing retraction of the upper lid. Very instructive in this connection are the observations made by Lang and Pringle (667) on 2 patients with Basedow's disease in whom, with absence of exophthalmia, the lid signs were developed in only one eye. After they had sprinkled cocaine in the other eye and when the gape of the lid aperture had increased following the full action of the drug, they became convinced that: 1. the gape was less pronounced than in the affected eye; 2 that disturbance took place in the consensual downward movement of the upper lid, and 3 the lower lid seemed to be drawn back somewhat below the level of the free edge of the lower lid of the other side. I have, myself, repeatedly had occasion to observe that the utmost gaping of the lid aperture occasioned by cocaine application never reached such a degree as that found often during pronounced retraction of the upper lid in Basedow's disease and furthermore, that the lower lid always shows a distinct retraction which never occurs to a noticeable degree in Basedow's disease (see above §43). Finally, I have never been able to discover the slightest indication of an inhibition of the accompanying movement of the upper lid during downward gaze. The decrease *in the frequency of blinking after treatment with drops* of cocaine is explained without difficulty by reduction or suspension of the sensitivity of the cornea When we add further that the signs shown in the lids in the rare cases of stimulation of the cervical *sympathicus* agree with those produced by cocaine, wherein however, the pupil enlargement also produced in the latter case is probably never absent, we have completed the evidence that can be brought forward in order to contradict the explanation of the lid sign as a result of a spasm of Muller's muscle. I only wish to point to the additional evidence already examined above in §54

§60. V. Stellwag (235) saw very clearly that a spasmodic condition of the organic lid muscles was unacceptable as an explanation of the lid signs which he had described He took refuge in the assumption of a reduction in resistance which the levator *palpabrae super* undergoes, that is, a decrease in tension in the circular muscle of the lids Since no diminution in *its apparent vigor or response to voluntary and consensual impulse* occurs it can only represent a weakening of those reflexes which, during the opening of the lids, act continually on the motor nerves of the muscles These reflexes close the lids from the sensitive conjunctival and corneal nerves, as well as from the retina. The infrequency and incompleteness of involuntary blinking which he discovered seemed to v Stellwag to point to weakening and occasional cessation of that reflex action. That this latter sign cannot, as in cocaine reaction, be traced back to the reduction of sensibility of the conjunctiva and cornea makes it plain that in the large majority of cases of Basedow's disease, and also in those in which the v. Stellwag

levators completely during sleep, and that in those instances where a gaping of the lid aperture is observed during sleep, the existing exophthalmia is responsible for this, this objection is probably based on an error In the cases of Chevallereau, Chaillous and Trug, in which every sign of an exophthalmia is lacking, the gape of the palpebral fissure remained not only during sleep, but, in the first cases, even during chloroform anesthesia (see above, §54). In certain cases as, for instance, the one which they had observed themselves in a 39 year old woman with retraction of the right upper lid and light ptosis on the left, Wilbrand and Saenger believe it is the result of an exaggerated tonus of the levator *palpebrae sup.* in Basedow's disease.

§63. In general, Wilbrand and Saenger held that the lid signs could be traced back to mechanical relationships which, in accordance with the individual differences in the anatomical structure, became more or less apparent in the number of cases under the influence of exophthalmia. Wilbrand and Saenger based their view chiefly on a diagnostic drawing found in Schwaller's *Anatomie der Sinnesorgane*[1] of a vertical section through the eyeball and orbit. This drawing deviates from actuality in more than one respect A wide thick band of fibers is represented which appears spread out between the lower surface of the levator and the *rectus superior*, so that Wilbrand and Saenger were led to speak of a "soldering together" of those two muscles. Furthermore they called attention to the individual differences which exist in the depth and space of enveloping folds of the conjunctiva If, now, this "soldering" were very firm, then during downward deviation of the eye the pull on the insertion of the *rectus superior* would be carried over to the levator and the chance be given to the upper lid at once to follow the downward movement of the bulbus But if this "soldering" were weaker and wider and if there extended a somewhat more yielding fold of mucous membrane into the *fornix conjunctivae*, toward which, from the levator outward, tendonous fibers radiate, then the eyeball could be somewhat advanced in its downward movement before the upper lid entered into this movement Indeed, it could even happen, with a moderate or slight increase in length of the levator, that, while the bulbus was making the movement downward, the eyelid would be drawn upward (Ramsay) at a certain moment It would follow naturally that this retrograde pulling action upon the upper lid would be much more evident when a protrusion of the eyeball was also present, by which, because of the pulling action of the eyeball, the levator tonus would be somewhat increased I must admit that this whole explanation makes a very convincing impression on the unprejudiced reader, especially in application to Ramsay's case which indi-

[1] Erlanger, 1887, p 221

any previous bias. They attributed the strong retraction of the upper lid to a spasm of the levator *palp. sup* muscle (see above, §13). Quite logically Lang and Pringle (667) have concluded from their experiments described above (§59), that the lid signs are to be explained by a state of tonic contraction of the levator *palp. sup* The cocaine experiments on a patient with Basedow's disease, mentioned in the same place, indicate the same to the unprejudiced judgment, as we have already pointed out above. In 1891 P J Mobius declared positively that the lid signs represent a stimulation phenomenon "the forces which keep the eye open during the waking state are stronger here than in healthy people There is, so to speak, an excessive tonus of the eye-opening muscles as in any excited person where it may be due to a transitory natural stimulation, or to mania, or to a maniacal condition" (p. 401). In 1896 he said (1478, p. 25) "The chief manifestation is evidently the tendency to a widening of the lid aperture, which counteracts the impulse to lower the lid"

L Bruns (1024) on the strength of his observations agreed entirely with the view of Mobius that v Graefe's sign is based on the tension of the eye opening, and that this tendency causes the insufficiency of associative movement of the upper lid in looking downward, but not at all in looking upward since it actually aids the raising of the lid and hinders only its lowering (p 12) This view seems to me also to be in full agreement with the clinical observations The above described observations of John Griffith (§43), of Ramsay, L Bruns, and Passler (§44) leave room for no other interpretation than that of a greatly increased "opening tension" of the eye And since, as we believe we have shown sufficiently, the smooth muscle innervated by the *sympathicus* cannot be considered as responsible for this, there remains only the assumption of an increased tonus in the levator *palp sup* Also, most of the cases in which the lid signs were found most fully developed with no Basedow's disease point with certainty to an increased or spastic state of tonus in the lid levators I would remind you especially of the retraction of the upper lids during mental excitement, (§54 and §55), the first case of Chevallereau and Chaillons, the cases of Chaillons and Trug (§54) and, furthermore, the observation of A. Pick (§55), Koppen and others

The close relationship of the three lid signs to one another follows naturally from this conception. As Mobius says, since there is a tendency toward widening of the lid aperture, the downward movement of the upper lid becomes difficult. Likewise this tendency acts to inhibit the execution of involuntary blinking, while during voluntary closure of lids it is overcome by the normally functioning orbicularis. When Wilbrand and Saenger (2033, p 46) offer, as an objection to the existence of a tonic levator contraction that patients with a conspicuous v Graefe's sign relax the lid

of fibers and are interspersed with numerous smaller and larger groups of fat cells. This bundle, richly provided with elastic fibers, radiates out toward the *fornix conjunctivae*, receives additions from the fascia of the *rectus superioris*, become somewhat heavier as they pass forward, and more from the fascia of the levator. Strong fiber connections which by crossing over, would pull from one muscle to the other, as Schwalbe's illustration suggests, do not occur A "soldering together" or a "firm connection" such as Fr Merkel and E. Kallius[3] mention cannot be admitted at all. The connection is always relatively loose. Also L Koenigstein stated in his *Notizen zur Anatomie und Physiologie der Orbita*,[4] that the muscle sheath of levator *p.s.* goes over into that of the *rectus superior* and binds it firmly with that muscle so that it could be separated from the former only with a scalpel (p. 21), and from the anatomical preparation one would *believe that the contraction of the one muscle must exert an effect on that* of the other muscle (p 31) This is true, however, only with the limitation that a slight shifting of one muscle over the other is at all possible only in the section from the equator bulbi toward the back. And even here microscopic study shows that there actually is a somewhat thicker, but not very firm, wavy fibrillar connective tissue layer, between the bundles, in these numerous groups of fat cells are interspersed with plentiful interweaving elastic fibers. That, aside from the action of the levator *p s*, even the simple contraction of the *rectus superior* is supposed to have the effect of raising the upper lid, is a supposition which one can grant only within certain limits

On the one hand, in cases with isolated ptosis, it is easily shown that downward deviation of gaze results in no appreciable elevation of the paralyzed upper lid. On the other hand, we know that during a gentle closure of lids the eyes are turned distinctly outward and upward (Bell's phenomenon) in a way which is not easily imaginable if a firm connection between the lid levators and the straight levators of the eyes acted in opposition to inhibit it. The well known fact that the upper lids accompany the upward and downward movements of the bulbi in a similar manner, is chiefly to be attributed to a neural association The influence of mechanical connection between the muscles involved is relatively slight To a certain degree, however, there is such a mechanical influence upon the position of the upper lid as demonstrated in certain clinical observations In a disturbance of the vertical balance of the eyes, the upper lid of the eye which is raised upward seems to be raised *somewhat more, and on the contrary* over the eye which is shifted downward a slightly lower position of the upper lid is noticeable This lower position becomes more apparent when

[3] This book, second ed , Part I, Vol I, Chapt I, 1901
[4] Beitrage zur Augenheilkunde, No 25, 1896.

cates an innervation disturbance with so much probability. (See §62 above.) But even the anatomical grounds on which the authors rely do not all correspond to the facts. I have before me some single sections, and some continuous series of sections of both newborn and adult individuals, which are taken perpendicularly, in the direction of the orbital axis through lid, eyeball and orbital contents. These permit not only the topographical relationship of the single parts to be studied but they also make possible an examination of the finer histological details. I would call attention to illustration 866 in Vol III of W Spaltholz's[1] *Hand-atlas der Anatomie des Menschen*, which was drawn from my preparation and is very well reproduced. In the newborn specimen from which the illustration is made, the small space between the anterior end of the *rectus superior* and the levator *palpebrae superior* is filled with a delicate, nucleus-rich, fibrillar connective tissue in which a number of larger and smaller cross sections of blood vessels can be seen. In this connective tissue in which the fibers run chiefly parallel to the surface of the two muscles, a fiber path stands out, without sharp boundaries. This breaks away from the fascia of the *rectus superior* at the point of attachment of the muscle into the tendon, and widening out fan-like, spreads to the upper *fornix conjunctivae*. (This fiber path stands out rather too sharply in the illustration.) A similar fascial peak branches out also from the connective tissue covering the *rectus inferior* and can be followed to the anterior surface of tarsus of the lower lid. From the side of this fascial peak, turned toward the eyeball, the already distinctly developed bundles of smooth muscle fibers of Muller's *M. palpebralis inferior* extend out. These attach themselves to the lower end of the articular disk of the lower lid. Inward and backward from this smooth muscle layer a connective tissue band stands out plainly which, branching out from the above mentioned fascial peak, runs to the lower pouch of the conjunctiva. From the upper lid the *palpebralis* muscle takes its origin, as is well known, at the point of fusion of the muscle tissue of the levator with its tendon. Indeed, single groups of spindle-shaped elements can still be followed among the final end branches of the striated muscle fibers. In several layers, laid one upon another and intersecting at sharp angles the bundles of the smooth muscle fiber, in adults often interspersed with groups of fat cells, run in a longitudinal direction diverging fan-like toward both sides in the direction of the convex border of the upper tarsus through its entire length. The connective tissue paths between the anterior end of the *rectus superior* and the levator *palp sup* and the Muller's *m. palpebralis* are, in the adult, denser, to be sure, and consist of single bundles, intersecting in various directions and filled with very numerous coarse as well as fine elastic fibers. The single bands come to connect with one another through an exchange

[1] Leipzig, S Hirzel, p. 792.

of fibers and are interspersed with numerous smaller and larger groups of fat cells. This bundle, richly provided with elastic fibers, radiates out toward the *fornix conjunctivae*, receives additions from the fascia of the *rectus superioris*, become somewhat heavier as they pass forward, and more from the fascia of the levator. Strong fiber connections which by crossing over, would pull from one muscle to the other, as Schwalbe's illustration suggests, do not occur. A "soldering together" or a "firm connection" such as Fr. Merkel and E. Kallius[3] mention cannot be admitted at all. The connection is always relatively loose. Also L Konigstein stated in his *Notizen zur Anatomie und Physiologie der Orbita*,[4] that the muscle sheath of levator *p s.* goes over into that of the *rectus superior* and binds it firmly with that muscle so that it could be separated from the former only with a scalpel (p. 21), and from the anatomical preparation one would believe that the contraction of the one muscle must exert an effect on that of the other muscle (p 31). This is true, however, only with the limitation that a slight shifting of one muscle over the other is at all possible only in the section from the equator bulbi toward the back. And even here microscopic study shows that there actually is a somewhat thicker, but not very firm, wavy fibrillar connective tissue layer, between the bundles; in these numerous groups of fat cells are interspersed with plentiful interweaving elastic fibers. That, aside from the action of the levator *p.s*, even the simple contraction of the *rectus superior* is supposed to have the effect of raising the upper lid, is a supposition which one can grant only within certain limits.

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the eye with the depressor paresis has keener vision and is used for fixation. The innervation impulse which is required to bring this eye into the horizontal plane of vision becomes apparent in the other eye in a more vigorous lowering of the bulb which the upper lid follows quite mechanically, so that a slight ptosis of this eye can be simulated. I am willing to admit that differences exist in the strength of the connective tissue bundles and in the wealth of groups of fat cells individually. That these were great enough, however, to force acceptance of Wilbrand and Saenger's explanation, I must certainly dispute, after what I myself have seen. On the other hand, the individual differences in the extent and depth of the enveloping folds of the conjunctiva are in fact so great and relatively frequent that, taken together with the supposed variations in firmness of the connection between eye and lid levators, they should bring to light v. Graefe's sign in persons without Basedow's disease far more often than they actually do. But in the clinical evidence on the lid signs there are also sufficient facts which cannot be brought into harmony with the views of Wilbrand and Saenger. The authors found themselves obliged to admit a tonus of the eye-opening muscles, raised by an excited state of the nervous system, as "a factor also aiding those mechanical relationships." I call attention to the not at all infrequent unilateral occurrence of the lid signs, either with or without exophthalmia (see above §48). The assumption of the authors mentioned that in Basedow's disease v. Graefe's sign is nearly always bilateral (2033, p. 44) is erroneous. It would be very strange furthermore if, in the anatomical relationships of the fascial connections and the pliability of the mucous membrane folds in the *fornix conjunctivae*, very considerable differences between the two sides should exist. In regard to the latter, since I started to pay attention to it I have never been able to determine any noticeable differences when the conjunctiva was in a healthy condition. On the other hand, an occurrence of unilateral innervation disturbances is not at all unusual. Still more decisive seem to me to be the changes in strength and extent so frequently observable in these very signs—the disappearance of one lid sign while the other continues, the appearance of one of the lid signs which was absent at first, all occurring without alteration in the protrusion of the eyes (see §45 and §51 above).

L. Ferri (1037) attributed the lid signs to the levator *palpebrae*, but denied an increased nervous stimulation. He tried to explain them mechanically and, in fact, in agreement with the origin of the exophthalmia,[1] by means of a vaso-motor paralysis of the orbital vessels, through an increased circulation in the muscle tissue whereby this would be shortened by purely mechanical means. Ferre's experiments on corpses, which were intended to prove this, are far from convincing. I believe that after

[1] We will concern ourselves with the explanation of *exophthalmus Basedowii* when discussing the pathogenesis of Basedow's disease.

giving the above description it will not be necessary for me to take time for refutation of this theory.

§64. If, in agreement with Mobius and L. Bruns we see in an increased tonus of the lid levators the essential explanation of the tendency to widening of the palpebral fissure during the occurrence of the lid signs, thus assuming the retraction of the upper lid to be, so to speak, the primary phenomenon, it could be argued against us that in many cases v. Graefe's sign may be found without the enormously wide gape of the lid aperture during straight forward gaze (see §15 above). When we look downward under normal conditions there follows, simultaneously with the innervation for the downward turning of the eyes, a relaxation of the levators of the bulb and of the upper lid, the latter glides downward as a result of the anatomical arrangement conforming with the downward turning of the eyeball. If, with extreme stimulation, the tonus in the levator which holds the upper lid at a particular level during horizontal gaze continues during the lowering of the gaze, and the tonus needed for relaxation of *the muscle is more or less incomplete or does not occur, then the phenomenon* called v Graefe's sign occurs

If we consider that the sustained tonus of the levator is increased with increased stretch of this muscle during the downward movement of the bulbus, then observations become understandable in which the upper lid suddenly jerks upward at the limit of downward movement (Ramsay §44, p 35). If an active innervation is added to the abnormally heightened tonus at the time of the impulse to look upward again, then it can happen that the upper lid springs up suddenly as in the cases of Passler and L. Bruns If, in the course of the disease the abnormal tonus in the levator of the lid increases still more, then, as observed by myself and others, the retraction of the upper lid, even when looking straight forward, will be added to v Graefe's sign Likewise, when improvement commences, the Dalrymple sign may disappear first, while v. Graefe's sign remains (Hinshelwood, §45) Cases also occur in which the abnormally increased opening tension of the eye continues although with downward gaze and with relaxing of tonus of the levator of the bulbus, the increased tonus of the levator *palpibrae sup* also relaxes enough to allow the lid to follow the downward turned eye Examples of this have been described above (see §45) The changeability in the occurrence and definiteness of the lid signs is not difficult to understand, using the explanation given The infrequency and incompleteness of involuntary blinking is also explained very well as we have already indicated above (see §62 above) by considering the extra tension of forces holding the eye open and the *increased tonus of the lid levators* This latter sign without the other lid signs seems to be found very rarely Only one case in the pertinent literature has come to my attention (see

§57 above) and this was complicated with hysteria. If at the same time a reduction of the sensitivity of the cornea exists (see §84 below), then this will, to be sure, exert an influence in reducing the number of closures of the lids The reason that we have fixed our attention on this continuous increased tonus does not belong here and will be taken up under the discussion of the pathogenesis of the disease.

§65. Several observers emphasize a peculiar, unusual stare exhibited, sometimes, in the eyes of sufferers from Basedow's disease. Even the very earliest observers mention this phenomenon (Romberg and Henoch 39, Stokes 46[1], Trousseau in several places, Virchow 200[2] and others). This exaggerated stare has been explained in the past by an increased moistening of the eyes, since in many cases tear secretion is pathologically increased (see §81 below) The basic cause of the unusual expression is, however, certainly to be sought in the group of signs just described, as briefly indicated above (§43) It is the lessened shading of the eyes by the lashes and the unaccustomed, strong light reflection, which, unmodified and seldom interrupted, streams out from the totally exposed cornea. In cases of Basedow's disease this gives the impression of intensified staring as, for instance when one is joyful "the eye beams", or, during scorn and anger, "the eyes are burning "

§66. We will now discuss a number of changes which appear in the eyes in cases of Basedow's disease It is true that these signs are not constant. Some merit our interest, although they are present only in exceptional cases.

Condition of the Pupils

§67. As a rule the condition of the pupils shows no change in size and reaction during the disease we are discussing. However, statements are not lacking regarding the enlargement of the pupils. This is usually described as slight and the light reflex remains intact Also, it cannot always be learned definitely whether the observer has taken into consideration sufficiently the fact that larger pupils are habitual in many people, especially during youth, in those who are anemic, and in those with severe myopia. On the other hand we frequently find smaller and also less quickly reacting pupils in old people and those under hypermetropic refraction conditions.

[1] "The eye is remarkably clear and translucent, in individual cases this gives them a sick look " p 231.

[2] The eyes, without being exactly exophthalmic, had an unusual secretion, p. 81, Note

Cases of Basedow's disease with abnormally large pupils were reported by Pauli (13) Romberg and Henoch (39), Roth (176) Geigel (181), Fournier and Oliver (190) and von Trousseau (219) in one observation of Cazalis W B Cheadle (223) saw widening of the pupils in 4 among 8 cases, Emmert (255) found the pupils in many patients larger, in others smaller than normal. In 1 among the 5 cases about which Eckervogt (516) reported, that of a 22 year old woman, the pupils were "very large," with good light-reaction S West (686) found once, among 38 cases, in a 22 year old girl, that both pupils were "a little enlarged" Among 22 cases Lewin (777) noted mydriasis twice and miosis 3 times Friedreich (191, p 312) found pronounced and permanent enlargement of the pupils in 1 among 6 cases Heymann (211) also observed it once In a 20 year old female patient reported by Jeunet (1740, p 37) there was a mydriasis The goiter was voluminous but soft, symmetrical, and accompanied the larynx in the swallowing movements Kocher (2197) found abnormal enlargement of the pupils only 3 times among 80 cases Gildemeister (136) observed, in one case, first mydriasis, later meiosis In a 32 year old woman, Russell (162) found a permanent narrowness of the pupils which was not perceptibly influenced by the action of light. Baumler (203, p 601) and Grancher (470) found the pupils smaller than normal; the latter found the left more narrowed than the right Buschan (1181) stated that he had "often enough" found the pupils narrowed On the contrary Knies (1123, p 461) said that a moderate enlargement of the pupils was often encountered, and according to Abadie (1808) the pupils were in fact usually larger than normal Sainton and Rathery (2973) observed in a patient with Basedow's disease who had recently given birth, a slight dilatation of both equally large pupils Eight weeks later the left pupil was somewhat larger than the right, and some days afterward the right seemed larger than the left This condition remained for six weeks Then both pupils again became equal, but remained somewhat larger than normal

After such varying statements it is of value to be able to point out that v. Graefe never observed an enormous enlargement of the pupils in any of the very large number of patients with Basedow's disease which he had opportunity to see. Likewise v. Stellwag (253, p. 50) says that he remembers no case in which a disturbance of the motility of the iris was found Eulenburg (334, p 82) found abnormal pupil enlargement always lacking in typical cases of Basedow's disease as did Schmidt-Rimpler (1785). Among 51 cases, very carefully studied, Passler (1362, p 229) found the pupils normal, reacting somewhat more quickly than usual and, with the exception of one case, equally large on the two sides. Also, in my 95 cases both pupils were of normal size and reacted well, with the exception of 2 patients In those 2 cases the right pupil was somewhat larger, and in 1 of these cases, that of a 27 year old woman, it was noticeable that the difference in the pupils was not equally pronounced at all times.

A more careful investigation showed that in this case the anisocoria was caused entirely by the inadequate light reflex of the pupil of the left eye. This showed a median width of 3 mm (measured by Haab). In the dark, the right pupil expanded in normal manner to a width of 7 or 8 mm. The difference was very striking In a certain medium illumination all differ-

ence disappeared, and with intensive illumination (looking toward a bright sky) the right pupil became smaller than the left. During convergence the left pupil reacted more slowly than the right The lid-closing reaction could be observed very plainly on *the left side* This peculiarity still continued when, one and one-half years after a goiter operation on the right side, most symptoms, and, above all, the general well being, had improved very considerably

Cases of anisocoria have been described many times in connection with Basedow's disease, but it must be remembered that slight differences in the size of the pupils are also observed sometimes in quite healthy people, that is, when a high degree of difference in refraction exists Mobius (1478, p. 27) expresses himself laconically when he says: "naturally differences in the pupils can occur in patients with Basedow's disease as well as in other people" In the majority of the cases under consideration the difference in the width of the pupils was only slight Furthermore, it cannot always be ascertained from the reports which pupil is to be looked upon as varying from the norm, the wider or the narrower one, in several cases views directly contrary to those of the author seems to me correct. How easy it is to deceive oneself about the true nature of pupil inequality without sufficiently careful examination is shown by our observation just described Several times grounds were present for considering pressure of a goiter lobe to be responsible for the anisocoria A few cases had unmistakable indications of a complication with *sympathicus* involvement (see §68 below)

Inequality of the pupils was mentioned by Robertson (339), Dyson (706), Davis (886), Schenk (938), Lasvienes (988) Eckervogt (516) noted in a 46 year old woman with a fist-sized goiter, chiefly affecting the right half of the thyroid gland, a "left pupil larger than the right" the large pulsating goiter apparently symmetrical S West (686) observed a slight pupil difference twice among 38 cases—in a 32 year old woman the left was larger, in a 35 year old woman the right was larger In 1 among 22 cases which Lewin (777) reports, that of a 36 year old woman, the left pupil was larger than the right. The goiter which made swallowing difficult for her was developed only on the right and on the right there were also signs of a vaso-motor paralysis of the nerves of the face It could well be the narrower right pupil which deviated from normal In the thyroid gland there was no distinguishable difference in the size of the two lobes Passler (1362) noted once among 51 cases a slight difference in the pupils, Ditisheim (1239) once among 17 cases The left pupil of a 34 year o [illegible]
saw in [illegible]
and later [illegible]
larged, the right lobe seemed somewhat more voluminous In the case of a 22 year old male patient of Hosslin (1450) the face was red and the left pupil was small An 18 year old woman with marked right-sided exophthalmia, a wide gape of the right lid aperture, and a *lag of the right upper eyelid*, Pfibram (2727), showed an enlargement of the right pupil In an acute case of Basedow's disease, a 41 year old woman reported by Foxwell (1433 and 1571), the left pupil was larger than the right. The

right half of the
have been the sm
old woman had a
duced compression symptoms of the trachea *Wilbrand and Saenger* (2033) found the right pupil smaller than the left In the other 38 cases pupil differences seem not to have been observed by these authors Among 80 cases Kocher (2197) saw a difference in the width of the pupils 3 times My two observations, which belong here, were mentioned above

A 29 year old male with Basedow's disease, a patient of *Roemheld* (2428), had in addition to abnormal size and inequality of the two pupils (the right had a diameter of 7 mm, the left of 5 5 mm) total light fixation and the so-called myotonic reaction, that is, in accommodation and convergence and in the test for lid-closing reaction they became relatively smaller quickly, and maximally, and remained abnormally long in this condition, finally enlarging again quite slowly, with varying alterations in form This phenomenon is rather rare and has been observed in various nervous diseases Whether there is any relation to Basedow's disease at all must probably remain undetermined.

Several cases of Basedow's disease have been observed in which fixation to light (Argyll-Robertson) with or without anisocoria, were complicated by other unquestionable signs of tabes (see §144 below)

§68. *In the following 5 cases still other characteristic signs of a unilateral sympathicus* affection, complicating Basedow's disease, occurred.

Eulenburg (226) in 1869 demonstrated before the Berlin Medical Society a young male patient who had a massive enlargement of the right half of the thyroid The gland was of a soft consistency with distinct bruit, tachycardia, palpitation, slight

old soldier with pulse variations of between 88 and 124 as reported by Chvostek (269) had a heavy carotid pulsation. His thyroid gland was moderately enlarged in all its parts The right pupil was definitely smaller than the left The right upper lid remained somewhat depressed and the right half of the face was more deeply reddened, warmer than the left, and covered with perspiration. A 60 year old man reported by E Fraenkel (305) also had a distinctly visible carotid pulsation, moder-

ing on the left side only, especially on the head The autopsy showed an enormous enlargement of the left thyroid lobe (up to 17 cm in length) It extended far beneath the sternum into the mediastinum and corresponded to a dullness distinguishable in that region The other lobe and the isthmus were only moderately enlarged The ganglia of the left *sympathicus* showed very striking changes In contradiction to the account of the authors we must probably here consider the *larger left pupil* and the wider left lid aperture as pathological A 38 year old woman patient of L. Jacobson (1739) had suffered from typical hemicrania since her 21st year and had a well

developed case of Basedow's disease Exophthalmia and lid signs were absent but there were characteristic manifestations of a paralysis of the cervical sympathicus of the left side The left pupil was about half as large as the right. Both reacted promptly to light and accommodation and upon darkening the eyes the left pupil was just as large as the right The left palpebral fissure seemed narrower than the right The upper lid remained somewhat low, but the lower one was also somewhat higher than the corresponding lid of the other side The left eyeball seemed to lie somewhat deeper in the socket (measurements are not given). While, furthermore, the right half of the face was reddened and felt moist or seemed covered with drops of perspiration, the left was pale and entirely dry This difference stood out in an especially conspicuous way when the patient was heated or inwardly much excited In conclusion, we present the report of Nitzelnadel (196) concerning a 47 year old male patient with the typical symptoms of Basedow's disease in whom the right pupil appeared larger than the left Furthermore, the patient complained of headache on the left side and said that he had often noticed severe perspiration on the left half of his face

In the first of these 5 cases the pupil inequality, and the further manifestations which complicated the symptom complex, may be traced back to a state of continual stimulation of the right cervical *sympathicus* The second, Frankel's case, has a right lateral paralysis of this nerve, a lesion of the left cervical *sympathicus*, established by anatomical examination We have before us the indications of a stimulation of the oculo-papillary fibres of this nerve, and a paralysis of its vasomotor and frenosudoral fibres (see #168 below) Something similar is observed in Jacobson's case, in which, together with the striking signs of a paralysis of the oculo-pupillary fibers of the left cervical *sympathicus*, the simultaneously occurring abnormal pallor and dryness of the left half of the face indicated a state of stimulation of the vasomotor and the frenosudoral fibers of the same nerve, unless we perfer to assume a paralysis of excitosudoral and vasodilatory fibers In Nitzelnadel's case a comprehension of the reciprocal relationships will be facilitated if we may assume that the left and smaller pupil is the one which is affected in its innervation We would then be dealing with a paretic condition of the pupil fibers which are components of the *sympathicus*, and with the sweat-inhibiting nerves

§69. Oser (601) observed a pupil inequality of an alternating type in a patient with Basedow's disease One day he found the left pupil larger and on another the right one Also Raehlamm (634) found in one case of Basedow's disease when there was a psychic disturbance, that sometimes the right pupil and sometimes the left was dilated.

Oscillating variation in pupil width during fixed gaze (wrongly called hippus) has been observed several times in Basedow's disease This manifestation also appears not infrequently in nervous individuals.

Kocher (2197) called attention to tremor of the iris as a "sign not previously described". I assume that he referred only to a chance observation

Behavior of Accommodation

§70. The function of accommodation of the eyes in Basedow's disease remains undisturbed in the great majority of cases. Indeed Trousseau

(219) emphasizes that in a severe case of a young lady with enormous exophthalmia, the adaptation of the eyes for various distances was excellent.[1] When, in severe forms of Basedow's disease we find a reduction in the power of accommodation combined with general weakness and exhaustion, and when perhaps asthenopic difficulty arises during long continued sewing work, we shall not be at all surprised. Marce (58), A v Graefe (63, p 291) and Laqueur (89, p. 10) already made similar discoveries Grancher reported (470), that a 37 year old man who had a blurr in his eyes during the height of Basedow's disease and who had to use convex glasses for reading, lost all symptoms of blurring when the other symptoms also began to improve. He could read again without glasses This is to be most easily interpreted by assuming an accommodation paresis with a moderate hypermetropic state of refraction. Exact data are not given and the spectroscopic findings are also absent. But when Diamoux (586) and his pupil Pedrono (632) state that accommodation disorders are almost always present in Basedow's disease, it is based on an error or an entirely uncritical interpretation of the symptoms observed Hansen Grut (593) states positively, on the other hand, he has never observed a weakness of accommodation in Basedow's disease We have often had an opportunity to convince ourselves that, in the state of great stimulation and nervous unrest found in many patients suffering from this disease, and with the difficulty of concentrating their attention for any length of time, it is always very precarious, and indeed sometimes impossible, to undertake an exact determination of the range of accommodation But when, after a few days or weeks, it had been possible to calm the patients we were able to determine that, with them as with all of our other cases, the position of the nearest point of clear vision just about corresponded to the age of the patient

Condition of the Retina

§71. O. Becker (270) in 1873, using the ophthalmoscope, discovered in the trunks of the retinal arteries peculiar phenomena which up to that time had not been observed In cases in which the phenomenon is well developed the retinal arteries are bound to be somewhat enlarged and one sees, especially in a study of the upright image, that not only in the region of the entrance of the optic nerve, but also extending more or less far into the retina small lateral movements occur in remarkable rapid sequence, synchronized with the radial pulse, whereby an increase in curvature of the vascular trunk alternates with an immediate subsequent stretching Simul-

[1] Ses yeux ont une propriété d'adaptation bien remarquable qui lui permet d'être myope ou presbyte à volonté

taneous with these, small variations in caliber can be perceived, comprising rhythmical expansions and contractions which are most distinctly recognizable in the main trunk before it divides. The locomotor changes can be seen best on the S-shaped arterial arch, while the wall reflexes perform the opposing movements at the oppositely curved section. These phenomena together and the motion of the arterial trunks in the retina, in some cases, are the only signs fully deserving the name of arterial pulse. This is doubtless to be distinguished from the pressure pulse which comes as intermittent inflow of blood through the *art centralis retinae* into the retina. This comes under observation through a rise of intraocular pressure and likewise is called a retinal arterial pulse.

Before the year 1873 O Becker had met with the retinal arterial pulse in 4 out of 6 patients with Basedow's disease In two cases with turbulent heart action, but without other abnormalities of the heart, the sign was displayed perfectly. In a third patient, a woman, the investigation was very difficult because of restlessness, but in spite of that the pulsations in the papillae as well as in the retina were demonstrated with certainty In the fourth patient, in whom the disease was already undergoing improvement, but with goiter and cardiac palpitation still continuing, spontaneous pulsations of the retinal arteries could be determined quite easily Of the 2 other patients, in whom no pulse signs could be found, the disease was, in one case, that of a 43 year old man, already well on the way to a cure, and the cardiac action had returned to normal In the other, because of an infection of the cornea of one eye, there was great restlessness and, in spite of artificial enlargement of the pupil, an exact investigation was impossible The arteries, also, did not appear to be enlarged Of the other 8 cases reported by Becker (453), 1880, 7 showed the phenomenon under discussion In a 28 year old woman with unilateral and intermittent exophthalmia, an arterial pulse extending far into the retina could be seen in the protruding left eye only, while it was entirely absent in the right

In three of his cases Becker emphasized especially that the arteries had very different diameters in different parts In several of his cases he observed a moderate enlargement of the diameters of the veins but variations of their caliber only once, in a 40 year old woman (453, p 2) The pattern of a general hyperemia of the *fundus oculi* was not found in any of these cases

Becker, in 1873, expressed the expectation that an exaggerated pulsation of the regional arteries would be found in all cases of Basedow's disease upon careful examination of the upright image This expectation, however, has by no means been fulfilled On the contrary we can say today that pulsation phenomena in the arteries of the retina, as described above, constitute very infrequent signs of Basedow's disease

It cannot well be assumed that earlier observers, like A. v Graefe (63, p. 292) Withuisen (73), v. Stellwag (235, p 30 and 33), and Emmert (255, 219), who described the findings of examinations with the ophthalmoscope, should simply have overlooked

the phenomenon The first of these observers emphasized expressly "that the retinal veins usually appear very wide and more winding than the norm" Also Withusen spoke of an increased fullness of the retinal vessels, and Emmert in several cases mentioned the width of the retinal veins, while the arteries were narrow. In a severe case of Basedow's disease in a 26 year old man, Andrews (230) using the ophthalmoscope found "a great hyperemia" of the fundus of the eye with enlargement of the arteries and plainly discernible pulse signs The veins seemed twice as wide as normal Also, after Becker had drawn attention to its frequent occurrence and had carefully described the manifestation, it was still found by only relatively few observers, and usually only in isolated cases

J. Hutchinson (312 and 321) observed pulse signs "in retinal vessels", which varied noticeably and, at certain times, were much more distinctly evident than at others. In a 27 year old woman Macnaughton (316) found, beside general enlargement of the retinal veins, distinct pulsation of the arteries in both eyes In the case of one female patient, H Cohn (Roesner 340, p 39) observed pulse phenomena in the two main arteries of the papilla which could not be discovered several days later V. Dusch (401) mentioned a retinal arterial pulse in a 13 year boy, and Eckervogt (516) noted the same in a 22 year old woman. In the latter case it was less distinctly developed; it was associated with engorgement of the veins and oedema of the papillae of the optic nerves of both eyes Gaill (514) tells of a case, an extremely emaciated woman, during the first attack of Basedow's disease no pulsation of the retinal arteries could be discovered, but during a relapse occurring two years later, a slight enlargement and pulsation of the retinal arteries and marked fullness of the veins could be distinguished After administering drops of homatropine, M Gunn (622) *observed pulsations of the veins of both papillae, and pulsations in the retinal arteries* of the left eye in the case of a 20 year old woman with typical Basedow's disease Rachlmann (634) has not found the arterial pulse absent in any of his 4 cases of Basedowism The retinal arteries seemed to be distended The movement could be followed for some distance into the retina A few times, in the region of the papilla, fluctuations in caliber could also be distinguished The veins were somewhat enlarged and were not pulsating Rachlmann's pupil, Friedrichson, (763) reports 2 more such observations In all 6 cases the unusually bright color of the blood was emphasized Westedt (871), among 6 cases which were examined with the opthalmoscope, has found the arterial pulse twice, once only weakly indicated, in these 2 cases the veins also pulsated Among 3 cases Liebrecht (916) saw, in 1 case, weak undulating movement in the peripheral branches of the retinal arteries E Berger (1088) mentioned pulsation of the arteries in the optic nerve papilla of a 55 year old woman In the case of a 22 year old anemic girl with a rudimentary form of Basedow's disease, Vossius (1387) reports that pulsations were seen in the retinal vessels almost to the end of the clinical observation Among 7 cases Franke (2372) found one with retinal artery pulsation which disappeared after the beginning of decided improvement (the result of thyroidectomy) Balacescu (2145) reported a 27 year old woman with typical Basedow's disease in whom the retinal veins were enlarged and the arteries in the region of the papilla were seen to pulsate Among Kocher's numerous cases (2197) a pulsation of the retinal arteries is noted in only one In the case of a 28 year old woman "the retina appeared in the ophthalmoscopic image somewhat enlarged, and distinct pulsation of the arteries were visible" In 2 among 46 cases of Basedow's disease, reported by B Donchin (2645) distinct arterial pulsation was discernible in the fundus of the eye One was a 36 year old woman whose vascular signs were very strikingly developed in the goiter, the other a 37 year old man who had a pulsation of the abdominal aorta and of the brachial artery R Stern

(2091) mentioned the occurrence of a retinal arterial pulse in only one of his numerous cases.

In most handbooks and monographs on Basedow's disease (Becker) the observations are simply quoted without the expression of an opinion founded upon original observations Only Berry (807) says, in his *Lehrbuch der Augenkrankheiten*, that, from his own observations, pulsations of the retinal arteries in Basedow's disease are encountered far less frequently than is assumed by some de Wecker (870) gives assurance in his Traité complet d'Ophthalmologie (p 924) that neither he nor Masselon, both experienced in recognizing the minutest details in the optic fundus, could ever, even with the greatest care, determine caliber vacillations in the retinal arteries during examination of the upright image in any of the numerous patients with Basedow's disease whom they had the opportunity to study It was always a shifting of the vascular light reflexes only, that is, of slight motion of the arterial vessels, such as we have described above, dependent on cardiac palpitations. De Wecker added also that the minuteness of the ophthalmoscopic changes in the eyes of such patients, even in those with a high degree of exophthalmia, always surprised him W. R. Gowers (1106) states simply, in his *Ophthalmoskopie*, that, in Basedow's disease the arteries are larger than normal and can hardly be distinguished in diameter from veins Concerning the pulsation he simply mentions Becker's observations but refrains from expressing his own opinion Schmidt-Rimpler explained, in his discussion of the diseases of the eyes in connection with other diseases (1786, p 376), that the sign described by Becker is only rarely to be observed, judging from his own experience with Basedow's disease More frequently one finds the retinal veins distended and tortuous In 1900 (2015) he repeated that he had observed the phenomenon in Basedow's disease only rarely Usually it is a case of slight movements, perceptible particularly at points where the arteries ramify. He added "usually a certain degree of good intention also is required to recognize the extremely delicate alterations as such" (p 277) Wilbrand and Saenger (3095) state that they had failed to see an arterial pulse in Basedow's disease quite as often as they had seen it elsewhere. In contradiction to this, Goldzieher (1967), a former pupil of O Becker, says in his *Therapie der Augenkrankheit* (p 417) that, in his experience, the sign is never absent, even to a slight degree, and therefore plays an important and differential diagnostic role According to his description it would seem primarily a matter of slight movements of the arterial vessels and slight shifts of the vascular light reflexes rather than caliber changes. All the cases of Basedow's disease which I, myself, have had an opportunity to observe have been subjected to careful ophthalmoscopic investigation; in the patients of the clinic and of the polyclinic results were always checked by a practiced assistant. Many patients could be tested repeatedly If a

reliable conclusion could not be drawn from the first examination, because of restlessness or excited condition of the patient, only a later diagnosis was taken into account. I am disregarding my earlier observations because no exact notations are at hand, and am confining myself to the 95 cases which I have studied during the past 12 years.

Three of these are excluded because suppuration of the cornea or a psychosis made use of the ophthalmoscope impossible. In the other 92 cases caliber fluctuations in the arteries of the retina could be recognized in only 2. Slight movements of the arterial vessels, recognizable in a slight sidewise shift of the reflex bands on the main arteries, sometimes only one of them, were observed in 9 cases. In 2 of these the phenomenon was discernible only in one eye, although the exophthalmia, only moderately developed, was equal on both sides In 1 case it could no longer be found, or was only slightly indicated, in the later examinations, although the state of the disease had not altered essentially. A fairly distinct venous pulse was noted in 12 cases, in 6 of them it accompanied the aforementioned manifestations in the arteries In the fulness and tortuosity of the retinal vessels no noteworthy variations from normal were observed

Dilatation of the arteries and veins without pulse manifestations was first observed by Fenwick (302 and 321), Easels, (405), Westedt (871) once among 6 cases, Ferri (1037), and Gowers (1106) Increased fullness, with or without a venous pulse was found by S West (686) in several of his 38 cases as well as by the aforementioned observers and by Wagenmann several times among the 51 cases of Pässler (1362) A venous pulse was mentioned by Fenwick (302), Fitzgerald (541), M Gunn (622), Carrington (651), Hill Griffith (658) 4 times among 28 cases, Westedt (871) once among 6 cases, Dittsheim (1293) once among 17 cases, by P Firdenberg (1308) in the left and only protruding eye, and by E V Hippel in Bettman's case (1406) Our own observations about this have already been mentioned above Whether a retinal venous pulse stands in close relationship to Basedow's disease is very doubtful It seems to me that it has been observed in this disease no more frequently than it is met with otherwise The observation of Fridenberg on the unilateral venous pulse with unilateral exophthalmia could, however, lead to the surmise of a certain relationship

The absence of any change in the circulatory system of the retina was emphasized by Yeo (396, Sotberg-Wels), Freudenberger (431), Murrell (474), Dianoux (586), Pedrono (632), Hill Griffith (658), S West (686), Maher (669), Huber (771), Westedt (871, 3 times among 6 cases), Lawford (915), Liebrecht (916, in 2 out of 6 cases), Lasvines (958), Dittsheim (1293, in all of his cases except one), Pässler (1362, in all but a few), Anderseh (1397), Mattiesen (1471), Franke (2372), Schulz (2118, in all of his 20 carefully observed cases), Kocher (2197, in all but one), Hoffbauer (2295) and G v Voss (2352, "veins only somewhat enlarged")

Nevertheless, it must be admitted that a retinal arterial pulse does occur more frequently than would appear from the above-mentioned observations These pulse manifestations, as mentioned several times, undergo fluctuations, these and other signs of Basedow's disease, especially of the cardiac palpitation, may disappear Only frequently repeated oph-

thalmoscopic examination would furnish conclusive evidence of the occurrence of the phenomenon or its total absence.

The visible pulse manifestations in the retinal arteries in healthy eyes and healthy circulatory systems are only very rarely to be observed and are very difficult to recognize Those illnesses in which they are found somewhat more frequently, and sometimes very clearly, especially insufficiency of the aortic valves and some cases of aortic aneurism can usually be excluded without special difficulty Recognition of a retina arterial pulse in doubtful cases of Basedow's disease can, therefore, still be of differential diagnostic value This usefulness will be only slightly diminished by the fact that the phenomenon occasionally occurs in chlorosis and in many cases of general anemia, and the latter, especially, is a conspicuous sign in many cases of Basedow's disease The arterial pulse in this illness, however, need be in no way dependent on an accompanying anemia. There are cases in which the phenomenon is developed most definitely in individuals who show no signs of anemia Becker has already described such cases Raehlmann attributes greater importance to the anemia In none of the 6 cases reported by himself and his pupil Fridrichson was this condition absent In several cases the skin pallor and that of the visible mucous membranes was striking. The bright red color of the blood in the retinal arteries was especially emphasized in all Pulsation signs in the retinal arteries were not caused by the vascular paralysis alone as Becker assumed, and not by a simple increase in the heart action This is shown by the fact that they are absent in carefully observed cases of pure vasoconstrictor paralysis, and are produced by an increase in heart action in very advanced hypertropy of the cardiac muscle without valve failure, or by bodily exertion Perhaps also a reduction in the elasticity of the arterial wall should be considered in connection with the origin of the retinal arterial pulse in Basedow's disease as first noted by Thoma [1] As a frequent consequence of chronic disturbances of the general nutrition, the inequalities in diameter of the retinal arteries, which Becker observed in 3 cases, may probably be attributed to a marked weakening of the vessel walls at definite places The visible pulsation observed in rare cases in the smaller peripheral vessels mentioned above (§16) may perhaps be attributed to a similar cause

Visual Acuity and Intraocular Diseases

§72. The faculty of vision, when there are no complications, is not affected by Basedow's disease Even with an extreme degree of exoph-

[1] Über die Elasticität du Netzhautarterien; Arch f Ophth, XXXV, 2, p 1.

thalmia it remains, as a rule, undisturbed. Isolated statements to the contrary are to be viewed with great scepticism. The statements of the patients alone cannot, of course, be given too much weight. An exact testing of functions cannot always be made during the first examination because of uneasiness and excitement, so that a definite judgment about the condition of the faculty of vision has to be postponed until later.

For example, in one of our patients, a 35 year old woman, not more than Vis 0.5 was reached during the first visual test After 8 weeks of treatment she had grown *considerably* quieter and could be tested with the usual ophthalmological methods of examination After correction for a myopic astigmatism, this patient recovered normal visual acuity in both eyes In all of our other patients with Basedow's disease except 8, in whom complications were present, the visual acuity was found to be completely or nearly normal after any existing *refractive disorders had been compensated* In 2 cases there was a high degree of myopia with patches of chorioretinitis in the fundus of the eye, twice *cataracta incipiens or nondum matura*, and 3 times *suppuration of the cornea*. In one girl the eye which was very convergent and squinted was amblyopic Hill Griffith (658) noted normal visual acuity 20 times among 32 cases In 10 of the others the inadequacy is explained by flecks on the cornea, a high degree of myopic astigmatism, etc In only two, the refraction test and the ophthalmoscopic examination resulted in negative findings

Ohlemann (2957), who himself suffered from Basedow's disease, observed bright scotomata which appeared only during strongly developed exophthalmia. He saw them only in the dark when he opened his eyes upon wakening in the night, especially during repeated wide opening and closing of the eyelids These bright scotomata were circular and radiating. When various observers state that the patients complain of not being able to carry on sustained work with the eyes, are blinded by light, or that their eyes become blurred, these are complaints we hear frequently from nervous and anemic persons without our being able, by examination, to determine any noteworthy decrease in accommodation or other objective changes.

Dianoux (586) believed that scotomata occurred very frequently as a result of injury to the optic nerve, stimulation phenomena, hyperasthenia of the retina etc Very soon thereafter signs of paralysis of the optic nerve and amblyopia would appear, sometimes developing into amaurosis Very often the signs are limited to those of stimulation or a slight paralysis with a reduction of the visual acuity to 0 2 or 0 1 The degree of visual disturbance can change with the fluctuations of the exophthalmia Sources of error, as shown above, for instance the slight alterations in the corneal *epithelium*, which must be taken into account, are not evident from the account of Dianoux and Pedrono (632) Sometimes injury to the optic nerve leads to a true neuritis, the traces of which can last a long time In the case of a 34 year old woman with pronounced Basedow's disease and severe exophthalmia, the visual acuity amounted to only 0 2 of normal Nothing is mentioned concerning the refraction of the eyes It cannot be learned whether an attempt was made to discover and correct a possible astigmatism It is only noted that the patient read (at what dis-

tance?) with 2 0 Jager No. 4, from which an accommodation paresis was diagnosed The outer limits of the field of vision were nearly normal, but the limits for green were greater than those for red The optic nerve papilla seemed very pale, yellowish, with indistinct contours In the course of nearly a year visual acuity decreased to less than 0 1, while the exophthalmia decreased noticeably and the general condition improved Hansen Grut (593) reported to Dianoux that he had never observed an amblyopia in Basedow's disease caused by that disease

§73. In the case of a 35 year old extremely myopic Negro, H. F. Suker (2769) observed extensive intraocular hemorrhages in addition to signs of Basedow's disease. Suker attributed this to the unusually high arterial tension which was found in this case (see §7 above).

§74. Edema of both optic papillae, with a slight "engorgement in the veins", and little pronounced arterial pulse was observed by Eckervogt (516) in a 22 year old patient Ramsay (1000) found, in 1 case, edema of the papilla without visual disturbance Rieger and V. Foster (500) observed in a female patient with Basedow's disease (Gowers (1042, page 260) in both papillae slight temporal edema. The capillary bed was congested and the disc contours completely blurred. The retina in this area showed no changes There was no basis for the assumption of an intracranial cause. In the case of a 28 year old woman Mooren (523 p 71) found the pattern of "a creeping *neuritis optica*" in both eyes He believed that this could be attributed to a complicating *syphilis hereditaria*. In the case of a 35 year old woman, Story (571) discovered a bilateral papillitis in the process of becoming atrophied There were also a few whitish regions scattered over the fundus, especially in the region of the posterior pole, and isolated pigment accumulations scattered along the course of the vessels. The visual acuity in both eyes amounted to $\frac{1}{6}$ of normal. Ferry (759) described a neuroretinitis in Basedow's disease and Hollis (902) noted a pronounced papillitis in both eyes in a highly anemic young woman with Basedow's disease Oppenheim (2107), in one of his cases, observed "neuritis optica" and assumed a chance complication In a 20 year old poorly nourished girl with conspicuous Basedow's disease, Friedham (2495) mentioned a moderate papillitis in both eyes After the removal of a goitrous right lobe the papillitis became reduced along with the improvement of the disease. In the follow-up examination, eight years after the operation, it could no longer be discovered, in spite of a slight relapse.

In a case described by Spalding (166) as Basedow's disease the pronounced pattern of a papillitis was observed simultaneously with a protrusion of the left eye With increase in the protrusion this eye became infected as had been the case four months before in the right eye A critical analysis of this case history shows, however, that if the existence of symptoms of Basedow's disease may be granted at all, the diplopia preceding the entire process as well as the enormous protrusion and

and the papillitis is to be related to a presumably syphilitic inflammatory process in the orbits.

§75. Atrophy of the optic nerve has been observed by Emmert (255) in 2 cases, by Rampoldi (603), in a 38 year old man, and by E. Pfluger (Salo Cohn 883, p 83) in a 55 year old woman Here the disease of the optic nerve can perhaps be traced to a facial erysipelas. In two other cases no perceptible complications were present. In the case of a 50 year old woman reported by Fridmann (2373), the beginning of an atrophy of the optic nerves was discovered in both eyes three years after the disappearance of a pronounced Basedow's disease This woman suffered from severe attacks of migraine (see below, §139).

There is a question as to whether the optic neuritis and optic atrophy observed in several cases of Basedow's disease without discernible complications stands in any direct relationship to that disease Isolated observations recently have been made on the appearance of *neuritis optica* and *atrophia nervi optica after long continued internal use of thyroid gland* preparations Coppez (1950) reported in the Société Belge d'Ophthalmologie, that he had encountered disorders in both eyes similar to those of a tobacco amblyopia, only more pronounced in the cases of five persons between 30 and 40 years of age, four women and one man who had been taking thyroid tablets in generous amounts, sometimes far more than the customary maximal dose, because of obesity The optic papilla often appeared somewhat hyperemic, the veins more tortuous, the arteries a little blurred There was a central scotoma with an intact peripheral field of vision. The visual difficulty began after the drug had been taken for several months, and it increased rapidly. Within six to eight weeks the vision diminished to 0 1 or less The prognosis was favorable according to Coppez's experience Following discontinuation of the medicine the power of vision returned, although sometimes only after three to four months The patients lost weight, a few of them as much as one-third of their former body weight, became nervous, easily fatigued, depressed, sleepless, and anorexic, but *otherwise showed no signs of hyperthyroidism, a fact which* probably encouraged them to continue the use of the medicine. An objection of Venneman that perhaps the phenomena in the eyes depended more on a general disturbance of nutrition than on the thyroid as such, does not seem to me to be justified Two years later Albertsberg (2140) made a report on a case of neuritis optica ending with optic atrophy following use of thyroid-gland because of myxedema

The 58 year old female patient took 0 1 to 0 5 grams of dried and powdered sheep thyroid daily After five weekly treatments the myxedema was considerably improved The body weight had decreased by about 10 kg and the pulse rate had risen from 100 to 120 beats per minute But otherwise there were no signs of hyper-thy-

roidism. The urine contained no abnormal elements Five weeks after the start of thyroid-gland medication the patient began to complain of decrease in sight of the left eye The visual disturbance increased rapidly Only nine days later, no light perception was left The ophthalmoscopic examination showed a diffuse redness of the papilla, tortuous distended veins, narrow arteries and isolated patches of white exudate Soon afterward visual acuity decreased to about 0 3 of normal. Color perception remained good An ophthalmoscopic examination gave the same finding as in the left eye but to a lesser extent. Whether the presence of a central scotoma was tested with enough small objects cannot be learned from the description Since no other cause for optic neuritis could be found, Albertsberg attributed it to the use of the thyroid gland After discontinuation of the medicine and therapy with potassium iodide the faculty of sight returned on the right to half of normal, but on the left it remained absent and the pattern of a beginning of *atrophia nervi optica* appeared To attribute the inflammation of the optic nerve to myxedema, as Schoute holds possible in his discussion of this case, seems to me entirely unjustified since the disorder of vision first made itself evident when the myxedema had already improved greatly

That more cases of visual disorders accompanying the extended use and misuse of thyroid gland preparations have not become known, however, is remarkable It could well be that slight degrees of such disorders have been overlooked, while the general malady, myxedema, cretinism, and other symptoms attracted attention. On the other hand, it is possible, as Coppez thinks, that many cases of socalled retrobulbar neuritis, the etiology of which remained unclear, are to be attributed to the use of thyroid

That in animals also, after prolonged use of thyroid preparations, a high degree of disturbance of visual function can be produced was first shown by an observation described by Coppez (1950).

A man gave to a dog which had grown too fat two tablets of Burroughs Wellcome's thyroidin daily. After a month the dog, a female, had grown much thinner but was almost blind Following withdrawal of the medication vision returned but was never quite as good again An ophthalmoscopic examination was not attempted.

Among the numerous experiments which have been made on animals to study the action of thyroid gland material, and active preparations made from it, we miss accounts of visual disorders. This can probably be explained on the one hand by the fact that such disorders are hardly noticeable in animals which are kept in confinement unless one pays special attention to it and that an ophthalmoscope test or anatomic examinations of the eye never were undertaken On the other hand, the large doses given produced the symptoms of a more or less severe thyroidism which entirely occupied the attention of the investigator I, therefore, directed my assistant, Professor A Birch-Hirschfeld, working with Dr. Nobuo-Inouye (246), to test this question, which is interesting in more than one respect and to determine the presence and nature of thyroid amblyopia by exact methods of experimentation.

Dogs of different ages and different breeds, after being weighed and found normal in regard to the fundus of the eye were given daily doses (8–10 gr) of thyroidin, small doses gradually increased The duration of the experiments varied between three and one-half and 10 months Aside from diarrhoea which lasted for a while, an accurate observation of the pulse respiration and body weight, together with repeated examinations of urine showed no signs of noteworthy disturbances in the general well-being Above all, no swelling of the thyroid gland could be discovered during life or at autopsy The histological changes which were found in one of the thyroid glands will be mentioned later (see Pathological Anatomy of Basedow's Disease) After several months of the feeding a distinct pallor of the optic papilla appeared in several of the experimental animals, this was associated with unaltered pupil reactions Signs of an inflammation of the optic nerve could not be definitely recognized in any of the cases, in spite of careful attention directed to it The pattern of atrophy included the entire optic disc and extended into the plainly narrowed retinal arteries An unmistakable visual disturbance could be demonstrated in only one dog five months after feeding was started The pupil reaction was retained As was to be expected from the previous observations on the action of thyroidin, great individual differences in tolerance for the poison were apparent in our dogs One dog showed neither clinically nor anatomically discernible eye disorder even after very long feeding (a total of 1670 gr) Others, after considerably smaller doses (32, or 345 gr) showed pronounced eye changes, as already noted, with no signs of a general thyroidism, just as in the clinical observations of Coppez and Albertsberg

Among 8 eyes which had been enucleated after varying periods of action *of the thyroid gland preparation, 6 showed the signs of atrophy of the* optic nerve in the ophthalmoscopic investigation, and in the anatomical examination the retina, the optic nerves showed a pronounced degeneration. In the retina this was evident (after intravital staining with methylene blue and Nissl-staining modified by Birch-Hirschfield with thionnerythrosin) in the chromatolysis of the ganglion cells, vacuolization and bloating of the cells, nuclear swelling, later nuclear shrinking, and finally cell disintegration. Among the relatively well preserved cells others were much changed The optic nerve showed partial, but rather extensive degeneration of the fibers with definite medullary degeneration (shown by using Marchi and Weigert stain) with no alterations in the glia, the connective tissue, or the walls of the blood vessels

It must also be mentioned here that W Edmunds (2172) using two monkeys which had been fed large doses of thyrocolloid, and which died on the seventh and twelfth days, could demonstrate parallel changes as shown in a very good illustration These changes were evident in the ganglion cells of the cerebral cortex, especially in the smaller cells, as well as in the ganglion cells of the medulla and anterior horn of the spinal cord, after using Nissl stain Only here the changes were, in general, further advanced Many cells were completely disintegrated and many free nuclei were to be seen Also, here certain cells were more affected than others Normal cells could be found, but only a few, and in many regions none The eyes were not examined anatomically with the ophthalmoscope

§76. Sometimes patients with Basedow's disease complain of *muscae volitantes*, a well known, remarkably common manifestation which in nervous and anemic cases can be especially troublesome Cloudiness of the vitreous body is mentioned in several cases, as by Leube (337, p. 29) and Mooren (317, p 15) They probably have no connection with Basedow's disease. Scintillating scotoma were noted by Roesner (340) in one case and by Kocher (2197) in a 39 year woman with conspicuous neurological signs

§77. Cataract has been found several times in Basedow's disease.

A case of Logetschnikow (991) affected both sides and had a not fully "ripe" cataract with a semi-hard nucleus This had developed in a 26 year old peasant woman in the course of several months of periodically recurring tetany attacks. In all there had been six attacks The onset of Basedow's disease dated back three years In this case the cataract formation is probably to be attributed to the tetany. Sacharjewski (606) mentioned a case of *cataracta senilis* in Basedow's disease and Vossius (2594) observed a developing cataract in a 49 year old female Basedow patient Among my own 95 cases I have found a gray cataract twice In one case, a 55 year old woman, I successfully removed the cataract from the left eye The cataract affected both eyes and had developed very slowly It consisted chiefly of nuclear sclerosis The margin showed only fine spike-shaped cloudiness, which extended to the anterior capsule At the time of the operation the vision of the right eye was V 1 5 to V 02, and on the left, with the same concave glass, V 01 Cortical vestiges remained which gradually became absorbed The last visual acuity noted was 0 3 after proper correction The goiter was small (neck circumference 35 cm) and chiefly affected the right thyroid gland lobe A pronounced exophthalmia was not present In a case of Logetschnikow a creeping iridocyclitis followed the removal of the cataract In Sacharjewski's patient the eye became destroyed by corneal suppuration after the removal of the cataract It may well be that in cases of Basedow's disease with great exhaustion, the low resistance to infection favors such unfortunate occurrences (see §93 below) In such cases the removal should be postponed until a more favorable time Exophthalmia as such, although it also makes the operation more difficult, in no way contra-indicates it, as we have already briefly mentioned above (§35) The open wound treatment as practiced in my clinic, must, in such cases, unquestionably be given preference According to my experience, a bandage in this case is even injurious

Because of the very frequent occurrence of gray cataracts this complication would necessarily come more often to notice if a close relationship existed between Basedow's disease and cataract development, even if we take into account that this illness arises most frequently during the later years of life, and cataracts in the middle years. Since infrequent miscellaneous tropic disorders in other structures of ectodermal origin are found in Basedow's disease (see §208 below) the possibility of such relationship is not to be discounted by any means.

Recently Vossius (2274) (2591) suggested a relationship between goiter and cataract, and has expressed the surmise that the clouding of the lens might be caused by disturbances in metabolism since these have been positively established in many thyroid gland affections. The cataract shows certain peculiarities It chiefly affects the nucleus and the circumnuclear layers, and has a rather firm coherence, so that it can well be disconnected *in toto* Of two patients with cataract who were recently operated upon in my clinic, and who were burdened with large goiters, the cataract in one of them, a 73 year old woman, showed the characteristics described above In the other, a 66 year old woman, it had comprised a thick grayish-white clouding of the lens reaching to the layer of the pupil Whether such connection really exists can be determined after long continued observations, especially in goiter regions The cataract might, perhaps, in such cases, be attributed to a simultaneous insufficiency of the epithelial rather than to the goitrous thyroid-gland changes

§78. There remains for us now to consider the statements about the origin of nearsightedness in Basedow's disease.

Prael (69, p 209) has made a vague statement on this subject Panas (496) later made the surprising report that a woman who had previously been emmetropic became myopic in the course of Basedow's disease. He spoke of the development of a myopia symptomatic of ophthalmia Dianoux and Pedrono (632) tried to explain it as follows: by the stretching and lengthening of the rectus eye muscles a lateral pressure was exerted on the eyeball and its anterior-posterior diameter was lengthened As early as 1857 A. v. Graefe (63, p. 291) stated quite definitely that he doubted, on theoretical grounds, whether shortsightedness resulted from exophthalmia Instead, farsightedness would necessarily result from the equal increase in the mass of the orbital contents on the one hand and of the pressure of the lids on the other He believed, therefore, that in regard to the supposed shortsightedness, errors in observation, or at least of interpretation, had been made. In one of his patients, to be sure, a well-developed myopia existed But it turned out that this had not only been present previously, but had actually become somewhat reduced during the exophthalmia In refutation of Dianoux, Hansen Grut (593) emphasized that he had never observed a change of refraction in the course of Basedow's disease Beard (1813) reported a considerable increase in an existing myopia of 5 0 D in a woman about 60 years of age, after she had developed pronounced Basedow's disease. Along with great emaciation the myopia increased on the left to 9 and on the right to 13 D, with a normal optic fundus. Urine was free from sugar After suitable treatment the general condition improved, but the degree of shortsightedness remained, as was to be expected Such a progress of myopia beyond 60 years of age is quite usual The general state of weakness, resulting perhaps from undesirable close work, makes this increase comprehensible Gowers (1042, p 259) has said that myopia seemed to develop in rare cases He explains further: it is probable that in

many cases, together with prominence, an actual enlargement of the bulbi exists, usually without any disturbance of visual function. Such an assumption must be most definitely contradicted with a criticism of R Stern's (2991) supposition that myopia occurs frequently in the kind of disease which he calls degenerative and "basedowoid" I refer to later explanations (see §244 below)

§79. Kast (912) together with Wilbrand studied the field of vision in 20 cases of Basedow's disease In all of them he found either considerable or slight limitation He believed it was significant in most of the cases since hysterical signs were absent Certain fluctuations occurring in the breadth of the visual field, Kast believes, should be considered comparable to the fluctuations which the other signs of Basedow's disease undergo Sougues (1006) then with Parmand, made measurements of the visual field of 12 Basedow's disease patients in the saltpeter works and found the visual field boundaries normal in 10 In the 2 cases in which a narrowing was shown, distinct signs of hysteria were present He therefore declared positively that concentric narrowing of the visual field was found in Basedow's disease only when there was simultaneous hysteria. The accounts of all later investigators also agree with this A narrowing of the visual field has also been discovered by Ballet (875) in a 33 year old man. This case was an especially significant example of a combination of Basedow's disease and hysteria (see §127 and §145 below) Fr. Muller (1134) attributed the visual-field narrowing which was found in one of his cases, in a 25 year old woman, to hysteria In a 52 year old woman E Berger (1088, p 108) found a narrowing of the visual field, but added "du à une hysterie concomitante" Mannheim (1222) noted, in 1 among 47 cases, a uniform contraction of the boundaries of the visual field in a 32 year old woman who had well defined signs of hysteria A case of concentric narrowing of the visual field of the right eye for white and colors was reported by Perregaux (1233) in a 19 year old man. At the same time there was a total hemianaesthesia of the right half of the body, a purely hysterical symptom Grohmann (1202) reported that, among 14 cases from the Gerhardt clinic, 2 showed narrowing of the visual field, one of them concentric, greater left than right; the other showed a temporary narrowing. Since nothing further is stated in detail it cannot be determined whether signs of hysteria were present. Possibly, this is simply because of lack of attention to it. In 1 among 22 cases whose history V. Mathes (3544) reported, a peripheral visual field limitation was established From the history of the case given by the patient it is learned that he had previously suffered from hysterical crises Schmidt-Rimpler (1786, p. 375) denied any pathogenomic significance of the concentric narrowing of visual field described by von Kast. In all the cases which he studied it was absent If there ever was any present it was

usually due to lack of attention, or to an early laxness of the same. Occasionally hysteria can also play a part. Schmidt-Rimpler in 1900 (2015) expressed himself similarly. I, myself, always found the visual field normal in the 22 cases in which it was tested.

§80. Gaill (511) mentioned in one case that with normal visual acuity and slight hypermetropia the tension of both eyeballs was definitely increased. The optic nerve papilla showed a physiological cup. Brailey and Eyre (1913) stated that an increased tension of the bulb is occasionally to be found in Basedow's disease and that it is made evident by the usual signs of increased tension, pulsation in the vessels (they probably meant the pressure pulse) hollowness of the optic cup, narrowing of the visual field, and reduction of the central visual acuity. In the 5 cases to which they refer all of which were female patients under 25 years of age, the increased tension was, as a rule, but not always, to be found in both eyes, and changed from time to time. There was a tendency to return to normal tension, however, under some circumstances, months or years later Also, the visual function usually returned to normal when the pressure decreased because the bulb walls in these young individuals had *sufficient elasticity* The observers attribute to this elasticity also the circumstance that the concavity of the optic papilla usually involves less than a fourth of the optic disc. It is evidently, therefore, only a physiological cup Also, concerning the field of vision they admit that in several cases the boundaries were not changed by the pathological increase in pressure to a degree which could be called a narrowing An estimate of the tension is made difficult in many cases by a soft swelling of the upper lids and the softness of the orbital tissue Bailey, therefore, recommended placing the finger at the side of the eyeball and supporting it while the finger of the other hand exerts a light pressure from the other side (from a written report) All the changes described are looked upon as consequences of the nervous and vascular disturbances which play such an important role in Basedow's disease I, myself, have recently tested the tension in all of my patients suffering from this disease and paid attention to the changes mentioned by Brailey and Eyre It usually affects patients aged between 19 and 30. In a few cases it seemed to me that the tension was somewhat less than usual and there was a weaker venous pulse The optic nerve papilla showed only a moderately large physiological concavity But in most of the patients the tension was certainly quite normal

Abnormalities of Tear Secretion

§81. Not infrequently at the beginning of Basedow's disease, lacrimation occurs without any local cause such as conjunctivitis or disturbance

of the tear ducts to which it might be attributed v. Stellwag (235) called attention to this overproduction of tears, especially in the early stages of the disease, as a frequent manifestation. Later E. Geiger (1088 and 2146) reported several cases in which lacrimation was the earliest indication of Basedow's disease, several times it preceded the other signs of this disease by some time There was either a continuous or a periodic flow of tears.

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the further symptom complex of Basedow's disease could be recognized. Also, there was increased sweat secretion The course was similar in a second case A 56 year old man, four years before, had been treated unsuccessfully for lacrimation by means of probing and astringent sprays He refused to allow extirpation of the palpebral tear gland Berger discovered slight bilateral exophthalmia and distinctly developed lid signs A closer examination then revealed the existence of palpitation, tachycardia and a tendency to sweating A stricture of the tear duct was absent, as in the previous case With improvement of the general malady, the lacrimation diminished In a third case tear flooding started in a 56 year old woman at intervals and always in both eyes, concurrent with sleeplessness and a series of nervous symptoms, as the first indications of Basedow's disease Exophthalmia was absent, v Graefe's sign, excessive sweating, and troublesome polyuria were present A 47 year old man who had always been nervous suddenly became subject to abundant lacrimation of the right eye At various times veritable attacks of excessive lacrimation occurred, mostly in the right eye, occasionally in the left, and sometimes in both. The examination of the nose showed no abnormalities Three years after the beginning of this attack which developed after strong emotional excitement, violent palpitation, rapid pulsation of the carotids, and polyuria developed From then on the pattern of Basedow's disease gradually took shape Often the patient was awakened from sleep by an attack of lacrimation with simultaneous palpitation and carotid pulsation In one case, observed in Paris by Verneau (2146), a troublesome lacrimation in both eyes was the only symptom for a long time After a year bilateral exophthalmia appeared, and 3 years later cardio-vascular signs were apparent In one case, from the Rothschild Spital in Paris, epiphora was one of the first and most troublesome symptoms of Basedow's disease In the case of a 25 year old male patient observed by Mathieu (1088) lacrimation began together with exophthalmia following a severe fright 10 years before It continued with the other symptoms of Basedow's disease after the exophthalmia had been absent for several years

Gifford (2666) reported a 27 year old woman who came to him because of swelling of the upper lids and excessive lacrimation The latter troubled the patient very much and was especially great when looking downward The woman had become nervous after the birth of a child eight months before Other signs included a slight swelling of the neck, a tachycardia up to 136 and a slight tremor of the hands Exophthalmia could not be definitely determined, but v Graefe's sign was probably present and there was great difficulty in turning back the upper lid (see §53 above). The position of the *punktum* was normal, as well as that of the lacrimal nasal duct A similar case also observed by Gifford was studied by Strader (2766), a 21 year old woman Swelling of the upper lids and a flow of tears confined to the right side were the first indications of Basedow's disease which led the patient to consult the doctor. The tear

flow was especially troublesome at night, when the patient lay in bed A disorder of the lacrimal canal was not found Awerbach (2801) also mentioned a case in a 37 year old woman in whom the tear flow and lid swelling confined to the right side was the only complaint Aside from a facial eczema nothing pathological was evident A month later v Graefe's sign appeared on the right (see §47 above) This, in combination with the one-sided lacrimation and the swelling of lids was the only basis upon which the diagnosis of Basedow's disease was established G Koster (1957, p 560) had frequently observed increased lacrimation in Basedow's disease even before the appearance of exophthalmia, or during its development

In 4 among Kocher's (2197) numerous cases, tearing was greatly increased without demonstrable local cause, 7 other patients with increased lacrimation suffered

beginning of her illness At the same time a "growing larger" of the eyes became noticeable. The exophthalmia was moderate (right 22, left 19 mm) and lid signs were absent *Conjunctivae and tear ducts were normal*

The tear flooding can be so extreme at times that the patients are greatly troubled by it It wakes them from sleep when such attacks occur at night (Schock (50), Romberg (Doeben, 53) Degranges (Fischer 75), Baumler (203, p. 598), Roth §341), Shingleton Smith (418)). A 45 year old woman who had suffered for eight years from Basedow's disease with bilateral exophthalmia and pronounced lid signs was observed by Wilbrand and Saenger (2146, p 137) She complained chiefly of a headache on the right side occurring every 2 weeks, and a troublesome tear flow which occurred in the right eye at night *only. As soon as she fell asleep the tears flowed* so abundantly that she woke up The tear flow never occurred in the day time. The attacks of dacryorrhea coincided in the main with the occurrence of the headaches on the right side That the tear flow is to be considered a purely reflex result of the headache, as Koster (2197, p 549) presumes, seems to me by no means certain, since the tear flow and the headache, as far as I can learn from the account of the observer, did not entirely coincide The patient of E. Berger who was wakened from sleep by attacks of lachrymation accompanied by strong carotid pulsation we have already discussed above v Stellwag (235, p 42) expressed the supposition that the tear flow in Basedow's disease is not caused by a direct pathological nerve affection, but by a reaction manifestation which corresponds to the strength of the impulse reaching the lachrymal nerves. The wide gape of the lid aperture in combination with the inadequacy of the involuntary lid movement must at first considerably increase the stimulation from the usual outer influences, and thus bring with it an increased secretion of tears To this is added *the not unimportant circumstance that, with* the infrequency and incompleteness of involuntary lid movement, the essential factor of the tear drainage must be considerably reduced in activity

I also (418) have supported this view in the past and a number of authors have adopted it; Render (789), Brandenburg (1177), Schmidt-Rimpler (1786), still believe that it is fully justified in certain cases. In the light of the observations of E Berger and several others described above, in which tear flooding in the absence of any other local cause preceded by a shorter or longer time, the appearance of the lid signs and exophthalmia or even was present to a very troublesome degree when these symptoms did not develop at all, there can be no question of a general application of that explanation

The occasional attacks of tear flooding, as for example during sleep, where, under normal conditions, tear secretion ceases, the coincidence of such attacks with unilateral headaches (Wilbrand and Saenger), or palpitation and increased pulsation of the carotids (E. Berger), point unmistably to a nervous origin of the tear flooding as a sort of secretion neurosis of the tear ducts Still, we cannot immediately adopt the further view of Berger, who sees in the epiphora of Basedow's disease a vasomotor neurosis of the *sympathicus*.

The findings from the animal experiments which show a participation of the *sympathicus* in the tear secretion still partially contradict one another Also, Campos has never been able to produce in monkeys the slightest tear secretion by stimulation of the *sympathicus* below the upper cervical ganglion Herbert Parson had the same experience G. Levinsohn, after a cutting through of the *sympathicus* in monkeys as well as extirpation of the upper cervical ganglion often observed immediately after the operation an increased tear flow This was no longer present on the following day, and he attributed this correctly to the great expansion of the vessels in the conjunctiva and in the lids occurring at the same time Furthermore, it is certain that, especially in regard to the innervation of the tear glands, the conditions in animals differ from those in man What we can look upon as definitely established is the fact that in man the secretory nerve fibres of the tear glands run in the path of the *facialis* of the ganglion *geniculi* Even if it is proved by the clinical evidence that the *facialis motor nucleus* cannot, at the same time, be the place of origin of the secretory fibres of the tear gland, but that this must probably be placed in the nuclear region of the IX cranial nerve (especially of the *portio intermedia Wrisbergi*) (Koster 1987, p. 543 and 2197, p. 533), yet the origin of these fibres from the vasomotor center of the *sympathicus* can be accepted most definitely

As to the question of how far, in man, an influence upon tear secretion is to be attributed to the *sympathicus* we have only a few reliable observations.

In the case of a female patient the upper cervical ganglion and a 24 cm long piece of the main trunk of the *sympathicus* had been removed by operation, one month later Campos found the eyes moistened normally Upon stimulation of the nasal mucous membrane tear flooding occurred Campos attributed almost the value of an experiment to this observation Jonnesco (1743 and Journ de Physiologie et de Pathologie générale, IV, p 845) following an extensive operation on the cervical *sympathicus* on both sides, found an increased tear flow together with congestion of the conjunctiva and increased secretion of the nasal mucous membranes and of the salivary glands In two patients examined by von Heiligenthal, *sympathicus* paralysis

resulted from a rapidly growing goiter; tear flooding occurred simultaneously with lowering of the upper lid In one of these cases there was a reddening of the conjunctiva and a purulent secretion. Probably the tear flooding was the result of the hyperaemia of the conjunctiva (see above—Levinson).

More exact investigations to solve this question were first undertaken by O Schirmer. Three patients had an operation on the ganglion *cervicale supremum* because of glaucoma Three cases had an unilateral, pre-existing paralysis of the *sympathicus*. He endeavored to determine the tear flow of each quantitatively by means of filter paper strips of definite breadth and length With 2 patients in whom the upper cervical ganglion was removed he could begin the stimulation experiments on the peripheral *sympathicus* stump directly after the operation Even a long continued stimulation with weak to medium strong induction current produced in man no increase in tear secretion, after section the volume of tears is always more or less reduced This reduction lasted from a few weeks to several months The quantity of the dry residue remained unaltered In a long standing *sympathicus* paralysis of several years duration, neither a quantitative nor a qualitative alteration of the tear secretion can be discovered

After this experiment it can no longer be doubted that the *sympathicus* bears a definite relationship to tear secretion and moreover, that it acts not in a roundabout way by acting upon the blood vessels of the glands but in a manner resembling the innervation of the salivary gland. It serves as an accessory to the predominant cerebral innervation, being a genuine secretion nerve although it cannot act independently to produce tear secretion

Let it be noted also that in the known cases of epiphora in Basedow's disease there has only once, in one case of Peugniez (Jeunet 1740, p 37) been a mention of a papillary enlargement

From this account it is clearly evident that the tear flooding in Basedow's disease cannot be looked upon as the expression of a *sympathicus* neurosis.

§82. In many cases of Basedow's disease especially in the later course of the malady, the eye appears less moist than normal The extent of this drying cannot be measured precisely In greatly protruding eyes, especially when the upper lid is considerably retracted, and the involuntary blinking is infrequent and incomplete, a lessened moistening of the broadly exposed eyeball surface will occur and will make itself evident by an unpleasant feeling of dryness Strong stimulation, rough wind, dust, smoke, etc , can, however, in such cases cause a flooding of the eyes with tears

In one case, that of a 56 year old woman with strong exophthalmia, a wide gape of the palpebral fissure and very infrequent incomplete blinking, v Stellwag (235, p 32) observed dullness and roughness of the speculum image, especially in the region of the cornea He concluded that there was a slight drying of the outermost epithelial layers A v Graefe (192) found a man with a slight protrusion of the eyes, scarcely exceeding the physiological degree, but with great retraction and lagging of the upper lid with

downward gaze In the left eye the lower half of the conjunctiva was edematous and protruded from the lid aperture There was a dry appearance and the lower corneal surface was dull (the right cornea had disintegrated due to suppuration) However, such cases are rare

That increased evaporation of the tears is not sufficient to explain the dryness of the eyes in all cases, is shown by an observation of Berger (1088, p 107) in the case of a 52 year old woman who had suffered for several years from Basedow's disease. In this case a decrease of moisture and a troublesome feeling of dryness developed while the protrusion of the eyes was beginning to diminish. In such cases we must probably seek the cause in a diminution of tear secretion This symptom can be brought about on the one hand by a reduction in the impulse for reflex secretion, on the other by a lowered activity of the gland itself whether due to reduced irritability of the secretory nerves, or to anatomical damage to the gland substance. An explanation of the diminished secretion by a disturbance in the sensory element of the reflex arc has been put forward several times by the authors C v Stellwag takes it for granted that the repeated action of irritants gradually dulls the sensitivity of the sensory nerves In those rare cases in which there is a slight drying of the outer epithelial layer of the cornea and conjunctiva bulbi, certainly no doubt can be cast on the insensitivity of the nerve endings Many observers consider the reduction of the sensitivity of the cornea and conjunctiva to be a frequent sign in the advanced stages of Basedow's disease and hesitate to derive the insufficient moistening from reduction of the reflexory tear secretion. I cannot uphold this view, at least not in such a generalized way, since it is my experience that the reduction of the conjunctival and corneal sensitivity seems to be very much less frequent than some authors assume, especially since it cannot always be shown in cases in which the patient complains of dryness of the eyes (see §84 below) Clear evidence is lacking as yet which would justify an assumption of a paresis of the secretory nerves of the tear ducts Nevertheless I would not cast it aside entirely The matter probably is not as simple as E. Berger (1088) pictures it; that the secretory nerves are in a state of stimulation at the beginning of Basedow's disease, and later on undergo an exhaustion. Cases in which tear secretion is reduced are not always preceded by a state of hypersecretion Microscopic studies are lacking completely However, it is noteworthy that Heusinger (38) found in one case that the tear glands, and in particular the right one, were almost half the normal size.

The explanation of the reduction of tear secretion due to a compression of the tear glands, given by A. v Graefe (63, page 289) in connection with the above mentioned evidence, seems to me unacceptable for more than one reason, and likewise that of de Wecker (879, p. 926) which accepts *une distention et une application trop*

forte du globe oculaire contre les canaux excréteurs des larmes as one of the causes for the dryness of the mucous membrane

§83. Goldzieher (1967) had occasional opportunity to observe that before the exophthalmia became noticeable a conspicuous hyperaemia of the conjunctiva sclerae was present which impelled the patient to consult an eye doctor. Signs of eye catarrh were then lacking In the further progress of the disease one often finds the *conjunctiva bulbi* netted with enlarged vessels and sometimes it goes as far as pronounced conjunctival inflammation with voluminous tear secretion and, for the most part only slight, mucous and pus secretion This can be very troublesome for the patient, but with mild treatment is quite susceptible to improvement However, it shows a great tendency to recur. In attacks of sudden flushing of the face so often observed in patients suffering from Basedow's disease (see §163 below) the conjuncitval vessels, according to my observation, usually take no part.

Abnormal Sensitivity of Conjunctiva and Cornea

§84. We have briefly indicated above that a reduction of sensitivity of the conjunctiva and cornea are frequently held to be a common phenomenon in the later phases of Basedow's disease The reduced moistening of the eyes and the feeling of dryness have been attributed to it They have also been used to explain the wide gape of the lid aperture and the infrequency and incompleteness of the involuntary blinking

A v Graefe (63, p 290) declared that a reduction of the corneal sensitivity was demonstrable in all advanced stages of the malady v. Dusch expressed himself similarly (207, p. 352) as did Emmert (255, p 219) and Pedrono (632) v Stellwag (235) had warned against a generalization from these observations In two out of his three cases the testing of the corneal sensitivity showed a normal condition in spite of the fact that the lid aperture, just as in all three cases, gaped widely and involuntary blinking "was almost entirely absent" Even in the 3 cases where the above mentioned dullness and roughness of the conjunctiva and cornea points to the assumption of a slight dryness of the epithelial layer, the patient perceived quite well touching and stroking with a feather and similar objects, without, however, reacting with defensive blinking. Cold damp weather caused lachrymation. I myself was not able, in any of my cases, excepting one with corneal suppuration, to demonstrate a clearly reduced sensitivity of the cornea However, extremely severe forms of the malady were not included Wilbrand and Saenger (2136, p 22) gave assurance, based on their observations, that a real reduction of the sensitivity of the cornea and conjunctiva in Basedow's disease is found only rarely There

is no doubt, however, that in severe cases, especially where there is a greatly reduced nutritional level, a reduction of conjunctival and corneal sensitivity can often be demonstrated. In cases in which reduced moistening of the surface of the eyeball exists, and as a result of dependence upon this, changes occur only slightly at first in the condition of the outer epithelial layers, these circumstances are sufficient to explain the dullness of sensitivity in the cornea.

A v Graefe (63, p 290) thought it probable that traction on the ciliary nerves during abrupt flexion at its turning point, an occurrence which takes place rather suddenly in the exophthalmia, brings about the reduction of the conductivity It is also possible, however, that a compression of these nerves by the swollen vessels of the fatty tissues, and later by the hyperplastic masses of the latter explain the facts In consideration of the fact that the *nervus opticus* undergoes no disturbance by stretching in Basedow's disease and that the ciliary nerves have a very winding course, it seems to me illogical to accept these tentative explanations, quite aside from the fact that, in most cases, the protrusion develops slowly and the elasticity of the orbital contents is by no means very great

It seems very probable that in cases in which a lowered sensitivity of the anterior surface of the eye exists, it will influence in consequence, retroactively, involuntary blinking and the degree of moisture of the eyes. It also plays an important role as determining factor in the origin of those sad, though fortunately rare, complications of corneal suppuration with which we shall now deal.

Corneal Maladies

§85. When disease of the cornea occurs in Basedow's disease it usually begins with the formation of isolated, small, indefinitely defined, grayish yellow superficial infiltrates in the region of the lid aperture, where the cornea, because of a high degree of exophthalmia and the strong retraction of the upper lid, is constantly uncovered, sometimes even during sleep. Above the spots of infiltration and around them the cornea appears dull. The infiltrations become enlarged, new ones appear, they blend into one another and form an ulcer which covers the lower third of the cornea, while the surface layers disintegrate necrotically. In severe cases the conjunctiva of the eyeball is strongly injected or protrudes between the lids as a red swelling A collection of pus appears in the anterior chamber and signs of inflammation are also found in the iris. In cases taking an unfavorable turn the suppuration and the ulcerative degeneration proceeds uninterrupted and often spreads over the whole cornea within a few days This results in a dissolution and casting off of a larger or smaller part of the cornea, with exposure and prolapse of the iris, sometimes with a casting out of the lens and a prolapse of the vitreous body. In many cases the

clouded part of the cornea within the continuously exposed region within the lid aperture has from the first a peculiar, dry, almost wax-like appearance. While the necrotic disintegration of the superficial corneal layers is taking place or even before, it changes without breaking through into a mass covered with brownish, thick, lamillated scabs.

Naumann (44) made such observations on both eyes of a 56 year old man, v. Graefe (63) on the right eye of a 38 year old man and (192) on the right eye of another patient; Prael (67) on both eyes of a man about 50, Cornwall (457) on both eyes of a 20 year old woman; Liebrecht (916) on both eyes of a 68 year old man, Jessop (1455) on both eyes of a 40 year old woman, and J Griffith (1728) on both eyes of a 21 year old woman.

In the majority of the cases, after the casting of necrotic tissue and after the following breakthrough of the cornea the process is completed by the formation of a flat scar and a more or less extensive healing of the iris Sometimes a corneal fistula remains for a time (Jessop-Power 1544, in the right eye of a female of 35, the left eye had been enucleated after a total suppuration of the cornea) In other cases, again, the exposed iris and the young scar tissue developed from it and from the bordering parts of the cornea bulge forwards and form into a scar or staphyloma (Nettleship 287, the right eye, Jessop 1455, both eyes of a 40 year old woman and others). Suppuration may extend to the uveal tract and result in an involvement of the entire eye contents, a panophthalmia.

In the first case of this sort which v Basedow (15, p 221) described, this was strikingly so In the case of a 50 year old woman both eyes became suppurated within half a year, causing great pain and "both stumps, having no anterior chamber, stood out like crab's eyes, between the widely spread protruding lids The scar of the cornea was covered with scabs and the conjunctiva, where it was not covered by the by the lids, was sarcomatose and swollen In both eyes lengthwise grooves were seen running from front to back caused by the tension of the recti, and dividing the bulbus into four protrusions, like the cords on a bale of goods " The condition appeared to be similar in a case of Hutchinson (664, p 38), a 21 year old very pale female who was brought to him after she had become completely blind In the cases of Lawrence (69) a 25 year old woman, of Jessop-Vernon (1455) a 24 year old woman, and of John Griffith (1728) a 21 year old woman, the eyes were enucleated because of intense pain and in order to shorten the process ' In the case of a 36 year old woman whom I observed myself, the bulbus contents were removed when the signs of the beginning of panophthalmia appeared

In many cases the whole process proceeded rather slowly with little pain, but in others it caused the greatest suffering (v. Basedow 15, Lawrence 69, Craig 1186, G. Griffith 1728 and others).

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It can also happen that infiltration by pus and ulcerative degeneration destroys only a part of the cornea. After or even without a circumscribed perforation it sometimes happens that a certain amount of visual function can be saved

This happened to a patient of v Graefe (63) in his late forties, in whom first the right, then the left eye was attacked, and formation of an artificial pupil offered a prospect for success, in the case of a lady of approximately 40 under Mooren's (523) treatment the upper portion of the cornea of the right eye remained and made possible the performance of an iridectomy, although the left eye was entirely disintegrated Similarly, in the case of a 52 year old man and a 41 year old woman under observation of Nettleship (1486) a tarsoraphia had been performed, another case was a 28 year old female patient of Churton (1029), and the left eye of a woman patient reported by Deschamps and Perriol (1558, and a 27 year old woman patient of Ch Oliver (Campbell Posey 1775) in whom, in spite of tarsoraphia performed early, the right cornea became almost completely ulcerated and the left one abscessed in the lower portion Another was a 54 year old female patient of Stern (2235) in whom during the early stages of Basedow's disease corneal suppuration occurred during a severe relapse Both corneas were affected by formation of abscesses The woman died of exhaustion a few months later I have myself had opportunity to observe such a case in a 21 year old female (see details §214)

Even with more favorable progress, when the infiltrates spread out only a little, or not at all and the abscesses caused by their disintegration clear up of themselves, the healing is delayed not infrequently because of a great susceptibility to entrance of further new infiltrates in the region of abscesses which are clearing up Finally, the transparency of the cornea is more or less affected.

Such was observed by v Graefe (63) in a 38 year old woman whose right cornea was totally ulcerated, Liebrecht (916) in a 68 year old man, in whom the right cornea was already destroyed, Jessop (1445) in a 24 year old woman, Rosenmeyer (1781) in a 45 year old man whose right eye could no longer be saved, and I, myself, in both eyes of a 21 year old woman

Rather mild forms of corneal disease in the form of single, smaller, suppurative infiltrates and abscesses in the region of the margin sometimes appear in Basedow's disease. Under suitable treatment or with improvement of the general malady they heal without permanent injury to the visual function.

I myself have seen such cases several times and other observers also report similar experiences, thus Langer (493) in a 45 year old man, Lutkemuller (521) in a 43 year old man, Andersch (1397) in a 65 year old man (in all 3 cases in the left eye) furthermore Patchett (275) in a 27 year old woman and O Becker (279) in a 23 year old woman, right, MacNaughton Jones (316) in both eyes of a 27 year old woman and Williams (346) in both eyes of a 40 year old woman, de Wecker (870) and Lawford (1464) one case in each, finally Gangon (352) and Nettleship (1486) in an 8 year old girl.

In one patient whose right cornea was entirely destroyed A. v. Graefe (192) found a marked *injection of the conjunctival vessels, a chemotic fold protruding from the lid aperture*, and the cornea dull over the lower half. Exophthalmia was very slight, and a suitable bandage led to healing without abscess formation A similar condition was observed by Nettleship (1486) in the right eye of a 52 year old man with high degree of exophthalmia whose left cornea was undergoing severe ulceration It healed after a suturing of the lids Zehender (238) saw a case with great exophthalmia and retraction of the upper lid in which the lower continually exposed third of the cornea was covered over with a thick pannus

§86. When we now inquire where we are to look for the cause of this ominous complication of Basedow's disease it seems most natural to attribute to the affection of the cornea a causal relationship with the inadequate covering of the eyes resulting from a high-degree exophthalmia as well as from great retraction of the upper lid and the infrequency and incompleteness of the involuntary blinking and the conditions resulting from this, that is, insufficient moistening and the reduced sensitivity of the corneal surface. It also cannot be doubted that this explanation is valid in many or indeed in the majority of the cases concerned The rather high degree of protrusion is usually emphasized expressly and in many cases especially conspicuous retraction of the upper lid is noted Several observers who could follow the process from the beginning, state that the cornea in the lid-aperture zone looked extremely dull and almost dry, and that its sensitivity was reduced

The nature of the corneal ulceration in Basedow's disease has been described as neuroparalytic In 1867, A. v. Graefe (192) following the views of Meissner, accepted at that time, classified it among those neuroparalytic corneal infections in which the "tropic" trigeminus fibers, rather than the sensory ones, failed to function Cornwall (457) also expressed himself in a similar way

Later, several authors characterized the corneal ulceration as *keratitis xerotica*, as did Jessop (1455, p 194), Schmidt-Rimpler (1786, p 373) Uhthoff (1921) This seems to me also to be the correct designation for a number of cases After a necrosis of the most superficial layers of tissue, caused by drying of the epithelium of the exposed part of the cornea, and a circumscribed inflammation caused by the chemical action of the decomposition products, the ground has been prepared for the establishment and growth of ulcerative microorganisms It is probable that these always play an important part in the processes with which we are dealing Through their spread and through the action of their toxic metabolic products the necrosis extends rapidly through tissues whose resistance is reduced because of the surface dryness This circumscribed ulcerous inflammation results in the casting off of a larger or smaller part of the cornea.

If the bacterial infection also extends to the uveal tract, then pan-

ophthalmia occurs, as has been seen elsewhere in connection with ulceration or infected wounds of the cornea. What types of bacteria are involved here or whether it concerns one special species has not, as yet, been investigated Incomplete corneal covering and superficial desiccation and their consequences are still by no means sufficient to explain all cases of corneal ulceration in Basedow's disease, as can be concluded from the following circumstances

1 The exophthalmia in a number of these cases, although only a small number, is only slight or its presence is not even certain

Such was the case in a patient of A v Graefe's (192), whose right cornea was completely destroyed To be sure, the upper lids were strongly retracted and did not follow the lowering of the plane of vision Perhaps the blinking was also infrequent and incomplete At that time (1967) no attention was paid to these signs A 68 year old female reported by Liebrecht had only a moderately severe exophthalmia The right cornea was changed to a yellowish, dry mass covered with scaly shreds, pus infiltrates increased in number and grew larger in the left cornea in a threatening manner Lawrence's (69) unfortunate 25 year old female patient had lost the left, greatly protruded eye with the greatest suffering, the right eye also became ulcerated a few weeks later with the same manifestations, although at this time it protruded to only a slight degree Mackenzie Davidson (1416) mentioned a case in which the ulceration extended over the entire surface of the cornea without any protrusion of the eye In a 51 year old man with very severe Basedow's disease observed by Hoor (2685) both corneas disintegrated by ulceration, and in a 50 year old woman patient of the same author this happened to the right cornea, although (in both cases) the eyes protruded only very moderately and could be completely covered by the lids

2. Ulceration of both corneas has been observed in cases in which there was no suggestion of dryness but, on the contrary, the cornea was flooded with tears (Baumler 203, in a 49 year old man, v Stellwag 235, p. 41, in an old lady) Also, in several cases, a purulent infiltration and ulceration of the cornea developed although it was protected from drying by a protective bandage worn continuously, or by a partial suturing of the edges of the lids Hoor, (2685), in a 51 year old man and a 50 year old woman, *(see §89 below)*, *Williams (346), in a 35 year old woman and a 40 year old* woman, Jessop (1455), in a 40 year old woman and W Campbell Posey (1755), in a 27 year old woman (see §89 below).

3. It was especially emphasized in several cases of corneal ulceration that the sensitivity was retained as long as the superficial layers were not thrown off; thus by Langer (493) in a mild case, by Liebrecht (916) in the left eye of the 68 year old man mentioned above, after a few small infiltrations had already appeared on the cornea, and by W. Jessop (1455) in his first case which ended in complete disintegration of both corneas. On the other hand, cases are known in which no further damage to the cornea

occurred during the entire course of the disease in spite of definite drying of the superficial epithelial layers and a great reduction of sensitivity, with very considerable exophthalmia, conspicuous retraction of the upper lids, and absence of normal involuntary blinking (v. Stellwag's 3 cases 235, p. 32).

Still other factors must probably be added to the above-mentioned harmful influences to bring about a deleterious affection of the cornea. In comparison with the thousands of observations on Basedow's disease showing marked exophthalmia and conspicuous lid signs, severe corneal affections are, nevertheless, very rare.

Among the numerous cases which Stokes (46), Trousseau, and Murray (3553, 180 cases) have seen, corneal ulceration was never found Among these were cases with unusually severe exophthalmia, indeed, Stokes (46, p 231) tells of a patient whose eyes had not been closed, even in sleep, for over a year, and yet no marked vascular injection of the conjunctival sclerae had developed Mooren (523), among 58 cases, saw only once, in a lady of about 38 years, an ulceration of the right cornea and an extensive abscess on the left Among 89 cases of Basedow's disease in the Leipsic medical clinic Roper (1911), during 10 years, reported only one, a 50 year old woman with ulceration of both corneas Among 73 cases with typical though partly incomplete symptom complexes of Basedow's disease Kocher (2197) tells of 3 cases, in which occurred the loss of one eye each and, in fact, always the right one, a 16 year old girl, a 22 year old woman, and a 40 year old woman In all three cases exophthalmia was considerable Among 95 cases which I myself observed, an ulceration of the entire cornea developed unilaterally only once A 36 year old woman developed hallucinations and insanity, after about an eight year period of Basedow's disease An abscess developed on the lower portion of the right cornea, spread rapidly, and ended with a breakthrough to destroy the whole membrane After the exenteration of the eyeball contents a definite turn for the better took place in the mental state as well as in the general condition A case has already been considered above in which both corneas were attacked by extensive persistent abscesses which, however, healed with formation of dense scars

§87. In the entire literature on Basedow's disease I have found 41 cases in which one of the eyes was lost, while the other was threatened with a more or less extensive process of ulceration Among these the right eye was severely involved 7 times. In 14 cases it amounted to a total ulceration of the cornea of one eye 11 times of the right and once of the left. in 2 it is not stated on which side it was Added to this are also 11 cases of corneal ulceration which A v Graefe (192) mentioned without going into greater detail besides those more accurately described from his own observations, so that we have to record altogether 75 cases of the loss of one or both eyes in Basedow's disease The very striking preponderance of deleterious corneal processes in the right eye is noteworthy Whether chance is responsible for this or special conditions are active can, at present, not be determined I only recall that in unequal exophthalmia a notice-

ably greater protrusion of the right eye beyond that of the left cannot be established. (see §33)

Moderately severe cases, in which the ulcerative process came to a close leaving extensive corneal scars, were observed 13 times, 7 times in both eyes, 6 times on one side.

In this connection I have taken up only those cases in which the diagnosis of Basedow's disease and the connection of the corneal ulceration with it seemed to me to be firmly established

Therefore, the case of Spalding (1661) already mentioned several times, was omitted, likewise a case of Wurdemann and Becker (2796) in which an ulcerative process in the ethmoidal cells and a degeneration of the hypophysis was present and death from meningitis with symptoms of a general sepsis followed, further a doubtful case of Berger (587) with ulceration of both eyes, finally a case of Warner (533) in a 25 year old woman with pronounced Basedow's disease in whom besides an ophthalmoplegia exterior there was also a paresis of the facialis and trigeminus These complications alone are enough to explain the formation of abscesses on the cornea

For completeness I mention also that in 44 cases of Basedow's disease a milder form of ulcerous *keratitis* has been described which healed without great or permanent damage In 5 cases both eyes were affected, in 9 cases one eye only I have, myself, observed such a form in the right eye of a 33 year old woman.

Reviewing the above summary the frequency of affection of both eyes is remarkable Among 65 cases of corneal ulceration, both eyes were affected with abscess formation in 51 In 10 of these one or both eyes escaped complete disintegration One was a 49 year old patient of Baumler (203) and this one was spared perhaps only because death intervened. In many cases both corneas were affected or already destroyed when the patients came under observation In others the interval between the attacks on the two eyes could be determined exactly It was usually very short

In the cases of a 35 year old female patient of Williams (346) and a 40 year old female patient of Jessop (1455) the interval was only two days In that of a lady of about 40 under Mooren's (523) observation it was three days In the first 2, cases the right eye was first attacked, in the latter case, the left In the case of a 50 year old woman patient, reported by Roper (1911), one week passed between the time the disease attacked the left and the right cornea In most of the other cases the ulceration of both corneas occurred within a few weeks, as in the cases of Prael (67, man of 50) Lawrence (69, 25 year old woman), Baumler (203, 49 year old man), Schwel
Saint-I
(1781, -- .
Stedman Bull (2048, 32 year old woman), Hoor (2685, 51 year old man with severe Basedow's disease) and in a case observed by me in a 21 year old woman In the case

of a 35 year old female patient of Jessop-Power (1455) the right eye underwent ulceration *three months after* beginning of the abscess formation of the left eye, and in the case of the 50 year old male patient of V Basedow (15) both eyes disintegrated totally in six months

§88. It is also noteworthy that in none of the known cases of corneal ulceration in Basedow's disease has any external possibly traumatic cause been given nor has any previously existing tear sac *blennorhea* been noted as a complication of the malady.

§89. A further unfortunate feature, characteristic of this corneal affection is, that in many cases we stand rather helpless, with only local therapy, before the advance of the process, and this is true not only, as de Wecker (870, p 927) believes, of the preantiseptic period. In a number of cases which have developed under the eyes of the doctor and from the beginning have been subjected to treatment by means of a protective bandage, suturing of the lid margins, sprinkling with antiseptic powder or bathing with antiseptic solution, scraping, cauterizing (Jessup's I case), lancing the abscess (Rosenmeyer), the process continued onward unceasingly up to the destruction of the entire cornea or the larger part of it In several cases ulceration began a few days after tarsoraphia was performed *on an entirely clear cornea*

Hoor (2685) in the very severe case of Basedow's disease of a 51 year old man kept the apparently normal and only slightly protruding left eye continually covered with

same observer a permanent bandage was at once applied when she visited the doctor because of a moderate *infection of the right eye In spite of this an infiltration* of the cornea very soon occurred which led to loss of the eye Eight days later signs of irritation appeared on the left eye Overnight a bandage was applied In the meantime it was possible to improve the general condition markedly and together with this the signs of irritation disappeared completely from the left eye

Williams (346) performed a tarsoraphia on a 35 year old female patient with entirely intact corneas but a high grade of exophthalmia This was at the patient's request and was done on purely cosmetic grounds 2 days after the operation, cloudiness and dullness of the cornea appeared, first on the right, later on left In spite of the fact that the lids were now completely closed by sutures through the skin folds, both eyes disintegrated through ulceration Also, on another 40 year old nervous female patient, with pronounced Basedow's disease and strongly protruding eyes, he performed the tarsoraphia chiefly for cosmetic considerations without anesthesia, although with effort both lids could be closed at the time and no inflammation of the conjunctiva or cornea was present On the second day after this minor operation reddening of the conjunctiva appeared together with a superficial infiltration of both corneas on the temporal border After immediate removal of the sutures and application of a bandage the process resulted, in this case, in healing, leaving behind slight marginal cloudiness

In the case of a 40 year old woman with enormous exophthalmia which made lid closure impossible Jessop (1455) sutured the borders of the lids at the outer corners of both the eyes to a distance of 4 mm, under chloroform One week later ulceration began at the cornea of the left eye, and ended with complete ulceration. W. Campbell Posey (1775) reported a 27 year old woman, studied by Ch. Oliver, with remarkably great protrusion of both eyes Although lid closure was quite impossible both corneas remained clear and shining for a long time. When the lower half of the right cornea began to cloud tarsoraphia was performed on both eyes However, after a few days the suture broke and the greater part of the cornea underwent necrosis. In the left eye also, in spite of the use of new sutures, the middle portion of the cornea became ulcerated The further outcome is not known as this patient withdrew from the treatment

In a 32 year old woman with a high degree of bilateral exophthalmia and the other major signs of Basedow's disease, Peters (2959) performed a tarsoraphia on the
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theless both corneas were destroyed On the left, the process was more swift and intensive

These sad experiences teach us in impressive fashion that the increase of the tension exerted by the suturing of the lid margins on the lateral corners of the lids and the increased pressure of the bulbi, which are pressed forward by the swelling orbital contents, influences the nutritive relationships of the cornea in the most harmful manner (see Therapy of Basedow's disease)

§90. A further item which seems to me to deserve full consideration is the fact that by far the greatest majority of cases of corneal ulceration involve severe cases of Basedow's disease

In the cases of not less than 12 patients under 63 years of age with total ulceration of one or both corneas death occurred within a relatively short time afterward, although a fatal outcome of Basedow's disease is, in general, rather rare

The known cases include a 50 year old male patient of v Basedow (15), the 49 year old man patient of Neumann (44), the 50 year old man patient of Prael (67), the 49 year old patient of Baumler (203), a 50 year old woman patient of Roeser (71), a 35 year old woman patient of Williams (346), a 35 year old woman under observation by Power and Jessup (1455), a 50 year old woman patient reported by Roper (1911) and a 51 year old gold worker whom Hoor (2685) observed In a 16 year old girl patient of Kocher (2197) in a rather good state of nutrition, but with a high degree of exophthalmia, and a wide gape of the lid aperture, the entire right eye disintegrated from corneal ulceration, death followed on the evening of the third day after the ligature of both upper-thyroid arteries and the left lower one In the case of a 40 year old woman with very severe Basedow's disease, in spite of tarsoraphia the right eye was lost, death came on the eleventh day after the ligation of the left upper thyroid artery and the surgical removal of a 4 cm long section of the left cer-

vical *sympathicus* In an unusual case of Schwekendiek (569), concerning a 2½ year old boy, death followed a few weeks after the ulceration of both eyes

Among the rest of the cases many of the patients were in very wretched condition at the time of the outbreak of the corneal affection or became greatly run down during its progress.

Such was the case with the two males reported by A v Graefe (63) in his first paper and likewise in Liebrecht's (916) 68 year male patient, and in Jessop's Ist and 2nd cases (1455) In the latter a psychosis developed after the ulceration of the second eye The 50 year old woman observed by Hoor (2685) developed an ulceration of the cornea of the right eye and was at that time unusually weak and emaciated A 44 year old woman patient of Wilks (345), who had lost the right eye from corneal ulceration, and a 54 year old woman with abscess of both eyes, observed by H Stern (2238), had Basedow's disease complicated by diabetes The latter patient died from exhaustion 5 months after the beginning of the illness

In several cases the deleterious corneal process came to a halt. This occurred only after a rapid and considerable turn for the better in the general condition

§91. Sometimes a corneal involvement appeared quite soon after the development of the symptom complex of Basedow's disease In other cases exophthalmia had been present for years before the cornea was affected by abscess formation

In the case of a pale, timid, 21 year old girl observed by John Griffith (1728), a small, superficial abscess was discovered on the right cornea just a few days after the first signs of Basedow's disease had been noticed At that time the lids could be closed easily From then on exophthalmia increased rapidly without, however, ever reaching an unusually high degree of development But the lids were so strongly retracted that even with great effort only a part of the cornea could be covered The destruction of the cornea advanced so rapidly that, seven weeks after the occurrence of the first signs of a keratitis, the right eye had to be enucleated and twelve days after that, the left eye

Uhthoff's series (2891) includes the extraordinary case of a 72 year old woman who had such a high grade bilateral protrusion of the eyes that the lids no longer closed A bilateral purulent keratitis with chemosis of the bulbar conjunctivae was the initial complaint which brought this patient to a physician. The other signs of Basedow's disease *were scarcely apparent at this time, although they developed in* the course of the subsequent observation

year old woman In the case of a lady in her late thirties Mooren (523) found a gray infiltration in the lower half of the left cornea six months after the onset of the disease. After three days this was partly ulcerated and the same ominous infiltration began in the right A 50 year old woman, about whom Roper (1911) tells, lost

both eyes by corneal ulceration about nine months after the development of Basedowism A 44 year old female patient of Wilks (345) had exophthalmia for a year. A 25 year old female patient of Hutchinson (664) was observed for a year and a half before an abscess formed on the cornea In the case of a 21 year old woman whom Leclerc-Saint-Lo (844) observed, gangrene of both corneas developed within a few weeks of each other three years after the onset of the disease In the case, which I observed myself, a 36 year old woman, exophthalmia had been present for eight or nine years Only after the development of a psychosis did an ulceration of the right cornea appear A 35 year old female patient of Power and Jessup (1455) after about a 16 year course of the disease, when goiter and cardiac palpitation were already considerably reduced and the general condition improved, developed an abscess on the left cornea during an influenza attack Five days later this led to the total ulceration of the eye (Also, in Prael's (67) patient it had existed a long time—more exact details are lacking) Only when the disease took a marked turn for the worse, which was indicated by increased weakness, occurrence of a feverish bronchial catarrh with mild delirium and frequent anxiety states, did the protrusion of the right eye increase considerably and the left eye begin to protrude too Now, for the first time a purulent infiltration in the lower half of the right cornea developed and a few weeks later it occurred on the left eye

§92. A v Graefe has called attention to the disproportionately large number of males suffering from the affections of the cornea He himself saw this ten times in men and only four times in women. From the evidence available up to now, however, an absolute predominance of the corneal ulceration in the male sex can not be claimed by any means Nevertheless there is, up to the present, a relative predominance As is known, the feminine sex is stricken with Basedow's disease about five times more often than the male, yet the corneal ulceration in women is not observed quite twice as often as in men.

Among 76 cases of total ulceration or severe injury to the cornea from abscesses in one or both eyes, in cases of which the sex has been noted, the male sex was involved 26 times and the female 48 times

Very notable is the additional fact that, among the male patients in whom the corneal ulceration developed by far the greater majority were of advanced age

If we omit Schwekendiek's unusual case (569) of a 2½ year old child, then, from among 16 men whose age was noted, there were 2 between 20 and 30 years, 2 between 31 and 40, 4 between 41 and 50, 5 between 51 and 60, and 3 had passed the 60th year of life (1 was 62 and 2 were 68 years old)

Therefore, three quarters of all destructive corneal disorders affect men beyond the fortieth year The greater frequency of the attacks of Basedow's disease falls, however, as we shall see, between the twentieth and fortieth year, for the male sex as well as for the female. Strange to say, this sad preference of the severe corneal ulceration for those of advanced age cannot be established at all in the female sex.

Incidence of 39 attacks of this ailment:
5 between the age of 16 and 20
14 between the age of 21 and 30
9 between the age of 31 and 40
5 between 41 and 50
4 between the age of 51 and 60
2 beyond 60

The highest morbidity figure for Basedow's disease and for corneal ulceration (three fifths of all cases) represents women in the same age period, that between the twentieth and fortieth year of life.

§93. From the preceding discussion it becomes evident *that the ulcerative* corneal process in Basedow's disease shows so many peculiar features that, as we have stated above, we are not satisfied with its designation as *keratitis neuroparalytica* or *xerotica* One probably must assume certain toxic substances circulating in the blood. In a severe form of Basedow's disease these toxins may reduce to a large extent the nutritional state of the corneal tissue together with its power of resistance to outer damage In the further course of the discussion we shall still meet with a series of manifestations and disturbances in Basedow's disease which support the assumption of toxic influence on the tissues and on the nervous central organs dependent upon these parts.

I wish to indicate here a peculiar corneal affection which has been observed in rare cases during experimentally produced acute or chronic *cachexia strumipriva* When the cornea is attacked a saturated, porcelain-like clouding usually appears, especially in the central part, with swelling *of the tissues and superficial abscess formation* I can, *without hesitation,* support the view of Leber who believes the starting point of this corneal involvement is a toxic endothelial necrosis Although, in the cases with which we are dealing, the nature of the poison is certainly a different one, yet analogous effects may here play a role which should not be underestimated.

Finally, it seems to me not irrelevant to recall that the corneal malady, known by the name of *keratomalacia,* which is seen not infrequently in very run-down individuals, especially in weak children a few weeks or months old, shows many point of resemblance in appearance and behavior to the necrosis and ulceration of the cornea, as it occurs in many cases of Basedow's disease. This corneal affection also is often considered a form of *keratitis neuroparalytica* or *xerotica* But here, too, usually no evidence can be found of the primary disturbance of sensitivity. Although, during sleep, many of these children do not fully close their eyes this is by no means the case with all of them Also, the reduced state of nutrition following digestive disturbance and frequent diarrhoea seems to me, taken alone,

not enough to explain the necrosis of the cornea. It must be a matter here of toxic influences originating from poisons which perhaps originate in the intestinal canal or which are formed in intermediary metabolism and reach the circulation by resorption Experience teaches that when, by suitable changes in nutrition, toxic substance can be gotten rid of and normal resorption conditions restored, not only can the fatal outcome be prevented but the corneal process may be very favorably influenced also, if it has not advanced too far.

In regard to the relatively frequent corneal ulceration in advanced age, especially in the male sex, it should be remembered that the nutrition of the cornea and therewith its resistance are unfavorably influenced, perhaps because of a higher degree of arteriosclerosis In a detailed report of an autopsy on a 56 year old male patient of Naumann (44, p 271) in whom both corneas had been destroyed, in great part, by ulceration, it is especially stated that the high grade atheromatose changes in the *cranial arteries extended into the art opthalmica* as well as into the *art centralis retinae* and even the *arteriae ciliares*

Insufficiency of Convergence

§94. In connection with the pathological changes which affect the eyes in Basedow's disease, we still have one more symptom to discuss This is an insufficiency of convergence and is usually designated as Mobius' sign

In the year 1883, on the basis of observations made on 2 patients with Basedow's disease who showed moderate exophthalmia equally on both sides, Mobius (559) called attention to a disorder of the convergence of the eyes In a third patient with exophthalmia this disorder was absent

Trousseau (128) however, seems to have seen something of the sort previously. In 1862 he wrote "fixer un objet est pour eux une difficulté et quelquefois une douleur". Indeed, as early as 1858 Withuisen (73) said of one of his patients that she experienced a certain difficulty in looking steadily at an object O Becker (279) as early as 1873 had turned his attention to the relationships of eye muscle balance in Basedow's disease and he expressly emphasized that in 4 of 6 cases in which these relationships could be tested, the muscle balance was not disturbed either for distant or for near vision Thus, evidently no insufficiency of convergence of the line of vision existed

Möbius came to speak of this symptom repeatedly in later publications Up to the year 1886 (673) he had seen it more or less distinctly 8 times out of 10 in patients with Basedow's disease In 1896 (1478, p 29) he said that it seemed to him that weakness of convergence was present in a majority of the cases

The best way to test the phenomenon is to have the patient focus the eyes on an object, for example the finger, in a horizontal or slightly lowered plane of vision. Then gradually bring the object nearer At a distance which in different patients as well as in the same patient differs at different times, but considerably farther from the eyes than for normal individuals,

the binocular focus will be lost. One eye turns outward during continued focussing of the other eye upon the approaching or moving object. Movements of the turned eye are parallel to the direction of view of the focussing eye Möbius (994) thinks that this sign shows most distinctly if one has the patient look first at the ceiling and then at his own nose As long as the convergence is still maintained many patients complain of a feeling of painful tension in the eyes and the forehead (compare also with Trousseau's statement above).

A Strümpell soon confirmed the observation of Möbius In the 3rd edition of his *Lehrbuch*, Vol II, p 141 he emphasized that he had seen this sign "repeatedly but by no means constantly, especially in patients with great exophthalmia" Charcot has likewise observed it, but declares it to be rare Moutet (852) mentions a 27 year old woman who had also a *nystagmus oscillatorius* (see §105 below) Upon the approach of an object in focus, the right eye turned outward, but did so without the occurrence of a diplopia O Kahler (775) confirmed that "the reduction of the power of convergence" was frequently demonstrable in Basedow's disease Among 7 cases from which he contributed a short quotation from the case histories (775a) he mentions it, however, only once—in a 36 year old woman. Eulenburg (825) considers the sign as rare, Leube (1127) expressed himself likewise in his special *Diagnosis of Internal Diseases* In the 6th edition (1901) he says, "not infrequently there is an insufficiency in the power of convergence" L Bruns observed, in 1892 (1024), in 2 patients with great exophthalmia a distinct weakness of convergence, in one case the right eye turned outward prematurely, in the other case the left one did so In a later publication (2668), he stated in general terms that he had often seen "the insufficiency of the recti interni" Fr Kraus (1870) considered insufficiency of convergence to be "a general characteristic not directly related to the exophthalmia" Among the 47 cases reported by Mannheim (1222), Möbius' sign in a more or less pronounced form was observed 24 times, was absent 13 times In 10 cases no notations on the subject were given Pässler (1362, p 228) who was quite aware of the sources of error in the testing of these signs and who tried to avoid them, found Möbius' sign unmistakably developed in 9 out of 51 carefully tested cases Among 18 cases reported by V Mikulicz and Reinbach (2010) it was mentioned 4 times Whether it was absent in the other cases, or simply had not been looked for, can not be learned, Ehrich (1959) noted it 3 times among 9 cases In 3 cases the absence of the sign is expressly mentioned Schulz (2118) observed it 6 times among 20 cases, and Kocher (2197) 28 times among his numerous cases, 31 times it was absent and in the others not mentioned K. Schultze (2749) reports that it was observed 7 times among Riedel's 50 cases, 6 times combined with other eye signs R Stern (2991, p 53) stated that he had noted this sign frequently Among 61 cases which Frank Billings (2806) reported, Möbius' sign could be demonstrated in only 5, in 7 among 8 male patients and 49 among 53 female patients it was absent My own experience has also shown that this sign is to be found only seldom in a well-developed form A more exact account will be given after we have examined critically its nature and significance (see below)

While Möbius usually expressed himself cautiously many others have proceeded very uncritically in judging this sign Möbius always spoke of impairment of the convergence while we find in several other authors'

not enough to explain the necrosis of the cornea. It must be a matter here of toxic influences originating from poisons which perhaps originate in the intestinal canal or which are formed in intermediary metabolism and reach the circulation by resorption. Experience teaches that when, by suitable changes in nutrition, toxic substance can be gotten rid of and normal resorption conditions restored, not only can the fatal outcome be prevented but the corneal process may be very favorably influenced also, if it has not advanced too far.

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§94. In connection with the pathological changes which affect the eyes in Basedow's disease, we still have one more symptom to discuss This is an insufficiency of convergence and is usually designated as Mobius' sign

In the year 1883, on the basis of observations made on 2 patients with Basedow's disease who showed moderate exophthalmia equally on both sides, Mobius (559) called attention to a disorder of the convergence of the eyes In a third patient with exophthalmia this disorder was absent

Trousseau (128) however, seems to have seen something of the sort previously. In 1862 he wrote "fixer un objet est pour eux une difficulté et quelquefois une douleur". Indeed, as early as 1858 Withuisen (73) said of one of his patients that she experienced a certain difficulty in looking steadily at an object O Becker (279) as early as 1873 had turned his attention to the relationships of eye muscle balance in Basedow's disease and he expressly emphasized that in 4 of 6 cases in which these relationships could be tested, the muscle balance was not disturbed either for distant or for near vision Thus, evidently no insufficiency of convergence of the line of vision existed

Mobius came to speak of this symptom repeatedly in later publications Up to the year 1886 (673) he had seen it more or less distinctly 8 times out of 10 in patients with Basedow's disease In 1896 (1478, p 29) he said that it seemed to him that weakness of convergence was present in a majority of the cases

The best way to test the phenomenon is to have the patient focus the eyes on an object, for example the finger, in a horizontal or slightly lowered plane of vision. Then gradually bring the object nearer At a distance which in different patients as well as in the same patient differs at different times, but considerably farther from the eyes than for normal individuals,

holding a prism with the edge upwards, or by means of a Maddox rod Probably those healthy people with protruding eyes of whom Mobius speaks belong partly in this category If such a person is attacked by Basedow's disease the previously discovered insufficiency of convergence will naturally not be classified as a sign of this illness

On the other hand attention should be called to the fact that we meet people, usually nearsighted, but among them also those with low-degree emmetropia and hypermetropia, who are able to focus by bringing an object up close to the end of the nose, thus showing no reduction of the width of convergence, and in whom, nevertheless, during fixation upon an object at 25 cm distance, a more or less important relative divergence is disclosed by the resulting distant double images. This is best shown by the method of Maddox These are, then, cases such as also occur, according to my observations, in Basedow's disease in which no "insufficiency of convergence" will be found by the commonly used methods Asthenopic difficulties may arise as a consequence of the tendency toward divergence. For such individuals are able to accomplish a high degree of convergence by means of forced fusion but are unable to continue it for long. One eye turns outward only, so to speak, after a longer or shorter futile struggle to hold the binocular single vision Those are patients who, if a correspondingly marked exophoria exists for distance also, can usually be helped only by an operative procedure: prolapse of the *rectus medialis* or tenotomy of the right lateralis.

As Mobius rightly emphasizes, patients in whom one or the other eye turns outward during a gradual approach of the finger upon which the gaze is fixed are not aware of the occurrence, and do not recognize any double image. This is by no means remarkable, because the line of vision of the eye which is turned away becomes directed more or less parallel to that of the focussing eye, as soon as the object has approached beyond the former convergence nearest point of clear vision, and the false image takes such an eccentric position that, as a rule, this does not cross the threshold of consciousness This is by no means always true as shown by a case of Sittman (1917) in which true double images were perceived during the test for Mobius' sign.

In nervous persons, neuraesthenics, and those with other types of weakness, the lateral shift of the fusion near the point for clear vision simultaneous with a reduction of the accommodation area is a phenomenon which can often be observed and is unrelated to age. In view of the general nervous exhaustion and bodily weakness of many patients with Basedow's disease it is certainly not surprising that they often display insufficiency of convergence. Kahler (775) considers Mobius' sign a "partial indication of the general nervous exhaustion peculiar to patients with

work the completely incorrect expression of an insufficiency of the *musculi recti interni* That the eye-muscles are certainly not very much weakened is shown plainly by the fact that in such cases the associated lateral movements are well executed to the extreme limits if there is no complication.

Mobius himself very correctly emphasized before that the insufficiency of convergence is developed to a degree that is not proportional to that of the exophthalmia. It can be absent when the protrusion is only slight or entirely absent and also during strongly developed exophthalmia On the other hand one cannot doubt that a high degree of protrusion of both bulbi favors a reduction of the function of convergence, since, as a result of the anatomical structure of the fulcra, the two eyes are pushed farther apart and therewith the difficulties in the mechanical conditions for the convergence movements increase

Mobius did not fail to test the convergence function in many patients with nervous ailments who had symptoms of Basedow's disease and no exophthalmia He stated (1352) that he had almost always found it undisturbed when there was an organic lesion. In those who were suffering from a state of weakened functions it was often distinctly reduced although never so pronouncedly as in Basedow's disease. It occurred to a higher degree in bulbar paralysis He has, no doubt wisely, left out of consideration cases with unilateral amblyopia. In fact, Mobius also admitted (1352, p 110) that he had sometimes come across an insufficiency of convergence "in healthy people with protruding eyes" and this was indeed quite the same as in patients suffering from Basedow's disease However, neither Mobius nor many others of the numerous observers who directed their attention to the sign have sufficiently considered the circumstance that insufficiency of the convergence is dependent to a certain degree upon the state of refraction of the eyes and occurs frequently with an uncorrected high myopia If it disappears upon correction of the myopia one cannot speak of an insufficiency of the convergence innervation or of the functional ability of the inner rectus muscles, for lateral deviation of one eye is the physiological consequence of the existing relationship between accomodation and convergence. In persons with a higher myopia than 10 D we sometimes find an insufficiency of convergence such as Mobius has described in patients with Basedow's disease in spite of the use of spectacles, and all the more so since a full correction for the near vision is often intolerable in such cases If there is a still greater difference in the degree of myopia between the two eyes a further factor is given, favoring an early lateral deviation of the strongly myopic eye upon the approach of the object Conspicuous insufficiency of convergence for distance is often demonstrated by methods which prevent binocular vision, for example by

Since, up to now, the above limitations were seldom if ever taken in consideration we must not be surprised at divergent statements about the frequency of Mobius' sign (see above). Therefore, most of them are without statistical value.

In the patients with Basedow's disease observed by myself the sign was always tested according to the above rules. A determination of the refraction of both eyes sciascopically and functionally, to determine the range of accommodation was never omitted. Note was always taken of the dynamic muscle relationships for distance and nearness, with and without correction of refraction or accommodation error, according to the method of Maddox.

Among 95 cases were 5 in which the sign could not be tested, once because of a unilateral corneal ulceration, twice because of strabismus which had been present since childhood (1 convergent with amblyopia of the left eye and 1 divergent), and once because of atrophy of one eye as the result of an injury In only 7 among the remaining 90 cases was an insufficiency of convergence observed which could be considered as a sign of Basedow's disease

A 56 year old woman had a rather marked exophthalmia The eyes were only weakly hypermetropic and turned upon gradual approach of the finger, as well as in the test of looking from ceiling to the tip of the nose, the right eye shifted laterally At a 25 cm distance with 2.5 correction a relative divergence of 9° (2½ M) occurred A 55 year old woman with very pronounced Basedow's disease but without exophthalmia, during gradual approach of the finger held as a point of focus, showed a deviation of one eye, usually the left, at a distance of about 17 cm Upon looking from ceiling to tip of nose the left eye always turned outward At a distance of 5 m the dynamic (absolute) divergence, with a myopia of 1 D, was only 2° At 25 cm however, a relative divergence of 15 to 18° was found The left eye, because of a beginning cataract, had less visual acuity (0 25) The patient claimed to see double often and even with her convex glasses of 2 D had difficulty in threading a needle A 17 year old female had always been called "nervously weak" but not by a hereditary trait *Protrusion of both eyes and swelling of the neck had been noticed for* 4 weeks Upon the slow approach of the finger in the horizontal plane to about 8 to 10 cm, that is to about the distance of the accommodation point, one of the eyes, usually the left, turned outward During the experiment of looking from the ceiling to the tip of the nose the left eye at once assumed the abduction position Concurrently there was normal visual acuity on both sides and very slight hypermetria, a dynamic convergence of 2° for distance, and for nearness a convergence excess of 4° The other cases showed nothing unusual

In two of our own cases the insufficiency of convergence was explained by high myopia of both eyes

In the case of an 18 year old girl with a myopia of 11 D there was a dynamic divergence of 10° for distance, and at 25 cm distance, a divergence of 15°, corrected by a 2 D vertical prism Here, therefore, the "insufficiency of convergence" is explained entirely by the abnormal resting position and the incomplete correction of the myopia for near vision In fact, by compensating the *rectus lateralis* of the right eye, which was usually turned outward, muscular equilibrium for distance was

Basedow's disease". Murray (2553) said he had observed weakness of convergence in a few of his 180 cases of Basedow's disease but did not find it pronounced enough to consider it as more than the indication of a slight muscle weakness Among the cases assembled by Roper (1911) Mobius' sign was found highly developed in one patient who was greatly depressed mentally, and who lay almost motionless, staring ahead, answering questions only very slowly and briefly, and who had to be fed because he refused nourishment.

The insufficiency of convergence, Mobius notes, does not, however, parallel the general weakness in Basedow's disease I can confirm this statement since I found in a bedridden woman suffering from severe Basedow's disease that the convergence function was still unaffected a few days before her death If any of the contributing factors described above leading to a difficulty of convergence are present, then this disease can bring out a latent insufficiency In general, if the strength of the innervation is weakened, it will become evident earlier when great demands are made upon the faculty of convergence. This, as Mobius correctly remarks, requires more effort than the associated lateral movements To this must be added, as we shall see later (see Pathological Anatomy of Basedow's disease), that the eye muscles are often affected by an interstitial fat infiltration and partial degeneration of the muscle fibers at least in the severe cases which end fatally While this seems not to become apparent or to show only slightly in the associated eye movements, (see §38) it may, in convergence movements, reach expression in a defect of function For example, it is not surprising that in nervous, more or less exhausted people, as many people afflicted with Basedow's disease are, an eye movement, unfamiliar to most people, like the transition of glance from the ceiling to the end of the nose, is incompletely executed. Also, during the test with the gradual approach of the fixation object the patient should be warned repeatedly to look fixedly at the finger Especially in the case of patients with Basedow's disease, it is not always easy to concentrate attention for any length of time. With a relaxation of the attention upon the object to be looked at, the eyes at once return to their resting position without necessarily showing an insufficiency of convergence The practiced observer at once notices this, however, because of the fact that both eyes turn outwards equally while with insufficiency of convergence present, one eye remains fixed and the other turns more or less outward

One may therefore begin to speak of an insufficiency of convergence as a sign of Basedow's disease when he has first oriented himself approximately with respect to the refraction state of both eyes, is able to exclude a high degree of dynamic convergence, and avoids sources of error in the examination itself.

Tremor

§95. Now that we have grouped together, for purposes of orderly discussion, the signs to be observed in the eyes and thus have had to consider many manifestations rarely or only exceptionally under observation in Basedow's disease, we shall now turn to the fourth main sign: tremor. In quite a number of cases in which tremor was plainly evident it did not escape the attention of earlier observers of the eighth decade of the past century. They included it in their description of the symptom complex of Basedow's disease To have pointed out the almost constant occurrence and the diagnostic importance of this sign and to have studied its characteristics carefully *in regard to rapidity, amplitude, and rhythm of* the trembling motions was, however, the service of Charcot and his talented pupil Pierre Marie He set forth the results of his investigation in 1883 in his now famous thesis (555)

In 1856, in his first report concerning the disease under discussion, which at the same time includes the first exhaustive description published in France, Charcot (55) had already called attention to the peculiar tremor In 1862 he reported (113) an 18 year old girl who, while still a child, had displayed a kind of *uncertainty in her* motions and a slight trembling of the hands A few days after marriage the well defined signs of Basedow's disease appeared, the trembling gradually extended over the entire body It became so intense that it made walking uncertain and wavering Aran (78) and Morell MacKenzie (211) also observed tremor of the limbs Chvostek (332) was impressed by the shaking of upper and lower extremities in two officers with pronounced Basedow's disease In another case (400), a 46 year old man, the tremor developed as the first sign of the disease, first in the upper and then in the lower extremities Raynaud (338) mentioned the trembling of the hands of a 25 year old woman, a tremor similar to that caused by alcoholism Rey (393) *referred to the* constant tremor of hands and head together with stormy heart action and general excitement as characteristic of Basedow's disease Douglas' (427) patient, a 34 year old female teacher, noticed herself that her fingers, when not supported, trembled constantly The tremor increased gradually and later also spread to the feet Guéneau de Mussy (492) observed, in 2 of his 4 cases, attacks of trembling of the extremities Delasiame (299) described in a 26 year old female patient a pronounced trembling extending over the whole body and most pronounced in the upper extremities, making posture and gait uncertain Benedict (348) declared that tremor in the extremities, especially in the arms, is a "common sign" of Basedow's disease Among 7 cases reported it was mentioned in 5 In 2 cases it was the first noticeable sign and was still continuing at the time of observation In 2 cases, the tremor was in the legs

General tremor, perceptible even when at rest, and stronger during movement was also determined by Féréol (303) in a 41 year old man with serious nervous complications (see §127) Likewise, J Russell (365 and 567) observed in one female patient a generalized tremor which came into play when the patient was standing upright or speaking Whynne Foot (467) mentioned, in one patient, a continuous marked tremor involving the entire body

established, and the relative divergence at the near point was reduced to 5° by corresponding closer to the nearest L point of clear vision by convergence. The projection of the eyes (19 mm distance of the corneal from the outer orbital margin) could not be attributed to the longitudinal form only

A 43 year old woman was sent to us for a more exact test of the eyes, with the notation "Mobius present" The examination showed a myopia of 15 D and a visual acuity of 0 1 for the right eye and for the left eye, with 15 0 cyl —2 0, a visual acuity of 0 2 was attained. At a distance of 5 mm a higher degree of exophoria could be demonstrated, and for nearness, there existed a manifest *strabismus divergens*, so that a Maddox test was not feasible any longer The moderate protrusion of the eyes, which likewise was miscalled a sign of Basedow's disease, could probably be entirely explained in this case by the considerable lengthening of the optic axis. The right lid aperture gaped more than the left and v Graefe's sign was more plainly developed on the right than on the left.

In the case of a 35 year old woman with equally great protrusion of the eyes on both sides and with lid signs only on the right, one of the eyes turned laterally when the patient tried to look first at the ceiling and then toward the end of the nose, upon the gradual approach of the finger, however, the convergence was retained almost up to the end of the nose With emmetropic refraction, equilibrium was present for distance, and for near there was a relative divergence of 2° Findings were similar in the case of a 33 year old woman with a myopia of 0 75 D, with no exophthalmia or lid signs, and in that of a 28 year old woman with slight astigmatism and a conspicuous angle γ But I have seen quite the same condition very frequently in entirely normal people with an emmetropic or slightly hypermetropic state of refraction The divergence determined for nearness was often somewhat greater, without, however, causing any asthenopia at all

In all the rest of my cases of Basedow's disease the faculty of convergence was unaffected in every respect. The refraction fluctuated around emmetropia: rather often a small degree of astigmatism was detectable in one or both eyes The test for the equilibrium of the eyes showed normal balance several times, a dynamic convergence once, a slight dynamic divergence of 1 to 4° In two cases, with intact convergence faculty and slight myopia or myopic astigmatism, this divergence was reached at 5°.

From my experience I must therefore state that insufficiency of convergence is a rather rare sign of Basedow's disease. I will, however, by no means assume that a somewhat more frequent occurrence could not be found by testing a still larger number of cases, taking into consideration all sources of error in the application of the tests

When the New York eye specialist, P Fridenberg (1305), says of his case, in which there was only a left-sided exophthalmia, that there was "an insufficiency of the inner rectus muscles of 5° for nearness" with 2° divergence at anatomical resting position and emmetropic state of refraction of both eyes, his case remains entirely within the limits which can be observed daily

Concerning the cases described as paralysis of convergence see §127 below.

recorded by Marey sphygmographs from the back of the hand, obtained the same results. The size of the excursions or amplitude of the single vibrations showed, as P Marie had already pointed out, a conspicuous changeability which, however, exhibits a certain regularity The oscillations increase in size until they reach a certain maximum and then decrease again to a minimum. Then they increase again. But these periods between one minimum and the next do not repeat themselves at equal time intervals and are not made up of an equal number of vibrations No relationship exists between this periodicity and the pulse or respiration. When he was suddenly called the excursions of the trembling motions in our patient increased considerably for a period of nearly two seconds and the number of the single, unevenly large oscillations increased somewhat, so that, during these two seconds, 11 oscillations, 7 larger and 4 smaller, were counted per second, while otherwise they came very regularly 9 or 10 per second including 2 or 3 small ones

The type of tremor described is so peculiar and constant for Basedow's disease that single exceptions tend to prove the rule

In a 41 year old man with Basedow's disease L Bruns (1021) observed a rapid trembling with small beats that were not so uniform in the sequence of the single oscillations In a 33 year old woman rapid small beats and rapid and fine oscillations alternated with slower and larger ones in which the single fingers participated in different ways, so that it often gives the impression of fibrillary twitching

Gowers (1042) probably stands alone when he states that muscle tremor in Basedow's disease is usually a rather coarse, rapid tremor which occurs only during movement

A comparison with curves taken from normal individuals shows the noteworthy fact that, in their essential characteristics, these curves exhibit a conspicuous resemblance to the type of tremor found in Basedow's disease Oscillations, eight or nine per second, occur with great regularity. Only their amplitude is regularly far smaller The aforementioned not entirely irregular variation in the size of the oscillations likewise should not be overlooked. It is, therefore, probably beyond doubt that tremors in healthy people, under the influence of certain psychic emotions, sudden fright, tense expectation, etc exhibit in type a complete agreement with the tremor in Basedow's disease On the other hand, the tremor in Basedow's disease frequently is so fine (see §98 below) that a tremor curve taken at such a period would seem to be almost identical with that of a normal individual The neurasthenic tremor and that of traumatic neurosis is of the same type It has the character of a rapid fine tremor increased or released by mental excitement It can be so violent that the patient is not able to carry a glass to the lips without spilling the contents

A Maude (1085) called attention to the fact that the tremor curve taken

The tremor is unequally strong in different cases, and also in one and the same individual at different times, sometimes extending over the entire body, more often confined to single parts It is usually most apparent in the hands and fingers when the hands are held, with the backs upward, stretched somewhat forward in horizontal direction and the fingers slightly spread apart Not only the hands and fingers tremble but the entire upper extremity Vibration is most noticeable in the fingers.

§96. The tremor in Basedow's disease is distinguished by rapidity and uniformity of sequence as well as by its relatively small amplitude or size of excursion Vibrations of the hands occur essentially only in a vertical direction Lateral oscillations or turns such as slight pronation or supination motions are not usually observed.

Moutet (843) stated that in his 27 year old female patient the trembling movements were chiefly lateral and the hands made slight turns around an imaginary axis passing through the thumb

The tremor in Basedow's disease is briefly characterized as a rapid trembling with small strokes. P. Marie (555) has graphically represented the first trembling motions of the hand by recording it from the *dorsum* or the *vola manus* outward, using, with proper precautions, a sensitive lever recording on a rotating drum covered with a layer of soot. Through the cooperation of S Garten, then assistant in the physiological institute here and with the friendly assistance of Birch-Hirschfeld, I obtained a vibration curve from one of our patients, a 28 year old woman with a pronounced tremor.

An attempt was made to obtain the curves in various ways 1) with the recording lever placed directly upon the volar side of the third phalanx of the free middle finger, 2) from the dorsal side of the free middle fingers while the recording lever was lightly attached to the fingernail with wax, the other fingers resting by their balls on the table surface, 3) by placing the recording lever upon the volar side of the lower arm with the dorsal side lying flat on the table surface In this method of recording, the size of the excursion of the trembling motion was relatively small Furthermore, several curves were recorded in such a way that, with the elbow supported, the ball of the middle finger was placed lightly upon the membrane of the drum, finally in such a way that the three middle fingers were placed upon a rubber ball connected with the Marey drum by a rubber tube, whereby a slight pressure on the rubber ball could raise the recording lever to a horizontal position

From the curves obtained in the latter manner, examples of the characteristic peculiarities of the trembling in Basedow's disease could be seen. These will be described here

With notable regularity eight to ten vibrations to the second occur. Huber (772) and Ditisheim (1293), who had their vibration movements

recorded by Marey sphygmographs from the back of the hand, obtained the same results The size of the excursions or amplitude of the single vibrations showed, as P. Marie had already pointed out, a conspicuous changeability which, however, exhibits a certain regularity. The oscillations increase in size until they reach a certain maximum and then decrease again to a minimum. Then they increase again. But these periods between one minimum and the next do not repeat themselves at equal time intervals and are not made up of an equal number of vibrations. No relationship exists between this periodicity and the pulse or respiration When he was suddenly called the excursions of the trembling motions in our patient increased considerably for a period of nearly two seconds and the number of the single, unevenly large oscillations increased somewhat, so that, during these two seconds, 11 oscillations, 7 larger and 4 smaller, were counted per second, while otherwise they came very regularly 9 or 10 per second including 2 or 3 small ones.

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[illegible]

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§97. Tremor is sometimes one of the earliest signs of Basedow's disease It sometimes precedes by months the development of the complete disease (Charcot, Marie, Gros 591, Dreyfus-Brisac 516, A. Lewin 777, Rosenblatt 1071, A. Maude 1058, Möbius in various places, Strumpell 1078 and 1918, Kocher 2197 and others).

§98. Sometimes the tremor is so faint that it is hardly noticed at rest and is first discovered when the hands are stretched forward in the manner described above. It appears more distinctly when the patients sit or stand than when they lie down An exceptional case, in which exactly the opposite occurred, is described by Kocher (2197) (see below §107)

Bodily exertion, especially under mental strain, in fact sometimes mere conversation about what disturbs the patient, intensifies or initiates it Although bodily rest does not always free the patient from his tremor with certainty, complete mental relaxation often accomplishes this P Marie observed, during coughing, an enlargement of the excursion of the tremor movements without perceptible alteration of their rhythm In Basedow's disease, in contrast to other forms of tremor, attempted movements do not intensify it. It can, however, if quite strongly developed, be very disturbing to such patients, so that threading a needle becomes impossible and every step is shaky (Marie 55, Ballet 535)

The occurrence of tremor handwriting is furthermore not very frequent in Basedow's disease because the tremor is not intensified under the influence of voluntary movement.

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To keep in mind the characteristic features of the various forms of tremor can be of greater importance in those cases of Basedow's disease in which goiter and exophthalmia are absent and in which tachycardia and tremor in combination with a few other inconstant findings furnish the only distinguishing disease signs to be found in the examination (see §244 below)

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I do not believe that such observations can lessen the diagnostically valuable significance of the peculiar tremor of Basedow's disease It need only be pointed out that the tremor develops sometimes before the tachycardia and can continue unaffected, while the latter improves, on the other hand the tremor at times can disappear entirely without any change in the rapid pulse.

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§99. In some cases the tremor affects the lower extremities also. It shows here most plainly *when the patients sit, and touch the floor only* with the toes. If it is more severe the whole body is seen to tremble when standing In severe cases or occasionally after great excitement the patients are scarcely able to stand, and walking becomes very difficult or at times almost impossible. (Charcot 113, P. Marie 555, S. West 686, Kocher 2197 in 3 of these cases, Lanz 2306.)

§100. In severe illness or during temporary exacerbation the tremor sometimes spreads over the entire body so that a hand laid upon the shoulder or the head of the patient perceives a shaking of the entire body. Such patients are, then, in constant vibration, sitting or standing

Beside the earlier cases, already mentioned, of Charcot, Delasiauve, Féréol, J. Russell and Whynne Foot, shaking of the whole body has been observed by Oppenheim (730) in a 46 year old man, by M Schmidt (1074) in a 32 year old man, by G. F Johnston (1120) in a 45 year old man, by E. Reymond (1143) in a 45 year old woman, by A J. Campbell (2157) in a 27 year old woman, by Peters (2561) in a 45 year old woman, by Stegmann (2582) in a 14 year old female, by Mannheim (1222) in 4 out of 47 cases, by Kocher (2197) in 10 out of 80 cases, and by myself in 4 out of 95 cases

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§101. Tremor is seldom more strongly pronounced on one side than on the other, and only exceptionally does it occur on one side only.

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§102. In some cases a trembling of the extended tongue is seen. When it is distinctly developed one can recognize that it is of the same character as the tremor of the hands

Trembling of the tongue was noted by A Lewin (777) 2 times among 22 carefully observed cases It was combined with tremor of the hands in a 17 year old boy and a 36 year old woman Such tremor was noted by Mannheim (1222) 10 times among 47 cases; it was combined with shaking of the hands or of the entire body; in one of these cases the tremor of the tongue was more severe than that of the extremities Among 17 cases from the Zurich Medical Clinic (Ditisheim (1203) the tremor of the extended tongue is mentioned 4 times, 1 time it was especially striking Hunerfauth (1735) reports about 3 cases of tongue tremor among 18 cases from the Kast Clinic V Mickulicz and Reimbach (2010) observed tremor of the tongue 3 times among 18 cases, Schulz (2118) once among 20 cases, and Kocher (2197) 19 times among 80 cases, among these it occurred twice without simultaneous tremor of the hands Among 95 of the cases observed by me the tongue tremor was noted 8 times

§103. Much more rarely, tremor of the lips or other facial muscles has been observed in Basedow's disease In the lips it can best be recognized when the mouth is puckered as if to whistle

Kocher (2197) saw tremor of the lips twice in a 40 year old woman together with a severe general tremor, and in a 22 year old woman with tremor of fingers and tongue It increased with speech Tremor of the facial muscles was observed 3 times among 27 cases collected by A Lewin (777) P. Millard (780) tells of a 58 year old man with Basedow's disease the tremor affected, beside the upper and lower extremities, also the facial muscles, the lips, and the tongue to such an extent that speech was trembling and stammering After 10 days of hospital care the tremor disappeared In Fr Muller's (1132) severe acute cases of Basedow's disease the tremor involved not only the hands, but also the mimetic muscle system of the face

§104. Sometimes one can distinguish a regular delicate trembling of the lids in patients with Basedow's disease if they are told to close the eyes lightly This vibration of the closed or half-closed eye lids, known under the name of the Rosenbach phenomenon, is really in no way characteristic of Basedow's disease, for it occurs to a pronounced degree in neurasthenics and indeed even in quite healthy people. It is met with in Basedow's disease not infrequently, if one pays attention to it Homén (835) stated that he sometimes had observed it in a slight degree in the lower lid According to the same observer it is rather variable, interrupted by a momentary pause or by a single larger jerk Sometimes such jerks occurred when the lids were not closed.

Tremor of the lids, with eyes closed, was mentioned by Mannheim (1222), Kitisheim (1203) and Kocher (2197) each of them once among their cases A. Lewin (777) stated that in a case of tremor of the facial muscles the eyelids were especially affected; whether with the lids closed or open cannot be determined G V. Voss (2352) mentioned a 31 year old woman patient with delicate tremor of the hands, severe

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the rapidity and fineness of the oscillations of the eyes agreed entirely with the nature of the trembling motions of the limbs Amblyopia was not present Renault (931) told of a 27 year old female patient with typical Basedow's disease in whom a nystagmus arose during the development of the disease, first weak, then more and more pronounced, so that the patient's vision was very much impeded Nothing is said, unfortunately, about the nature of the eye tremor *L. Bruns* (1024) *mentioned*, concerning one of his cases (a 33 year old woman) that the eyes, with an expression of unthinkingly looking far away, began to tremble when they remained quiet in fixation *It was a matter of rapid, finely oscillating trembling movements In a 22* year old woman with severe Basedow's disease G V Voss (2352) observed fine, nystagmuslike twitching upon movement of the eyeballs, together with a severe general tremor During a later relapse paralysis of the eye muscles was evident (see §127 below)

Among Kocher's (2197) numerous cases tremor of the bulbi was observed 8 times Nothing more definite is stated about the kind of tremor In a 22 year old woman in whom something anxious and unsteady *in the facial expression was noticeable*, a nystagmus occurred upon looking upward In 2 of Riedel's 50 cases (K Schultze 2749) a slight trembling of the bulbi was observed Kroug (2700) saw nystagmus 3 times among his 106 cases Whether this was really to be looked upon as one of the signs belonging to Basedow's disease cannot be learned from the description

For the detailed description of a peculiar case of *nystagmus oscillatorius* in Basedow's disease with an incomplete symptom complex we are indebted to C S Freund (957) It concerns a 19 year old male locksmith who, during his military service period, was attacked by an eye tremor in the morning on awakening after he had taken part in a very exhausting field service drill the previous evening The oscillations were small and so rapid that their frequency could not be counted They caused uncommonly rapid apparent movements of the object, a back and forth shaking and glimmering which was very disturbing to the patient The frequency of the oscillations was considerably reduced upon strong convergence, and at the end points of lateral movements A complete cessation of the nystagmus was accomplished when fixation was permitted with one eye only Furthermore, there was a very rapid vibration of short duration, at intervals of 1 or 2 seconds, involving the upper eyelids This was caused to disappear by firm pressure The further examination showed a rapid pulse of 110 beats per minute, some cardiac arrhythmia, and a small goiter There were also periodic attacks of profuse watery diarrhoea and increased sweating Tremor of the extremities was entirely absent, as was exophthalmia Very peculiar was the behavior of the nystagmus in response to electric current While this ordinarily has no effect upon nystagmus, in this case, after the action of a current of about 4 MA with the anode above the eye region and the cathode on the neck, a considerable reduction in the force of the tremor could be recognized At the end of the first sitting, a period of five minutes, it had almost ceased. After eight days of *treatment every trace of nystagmus had disappeared, and gradually* the other signs also diminished After two slight recurrences of the eye tremor, during which rotating as well as horizontal oscillations occurred, the patient remained permanently cured Freund emphasized especially that he found no indications of hysteria I have no hesitation in considering the nystagmus in this case, as in the one previously described, as analogous with the tremor of the extremities and a genuine sign of Basedow's disease. P J Möbius, who in 1891 (994) believed that the nystagmus in Freund's case should be attributed to hysteria, later wavered (1478) in this opinion It was quite otherwise in a case of nystagmus about which Mannheim

shaking of the left leg, and tremor of the eyelids. I, myself, observed, several times distinct trembling of the upper lids upon lid closure and once upon lowering of the plane of vision

We may explain the Rosenbach sign, as Wilbrand and Saenger (2033) do, by the opposition of forces. *From the upward and lateral movement* of the eyeball with lid closure, as a result of fascial connection between the *rectus superior* and the levator *palpebrae superior* on the one side and the pouch of the transitional fold on the other side, a certain pull is exerted on the upper lid The lid-closing muscle has to furnish a balance. It is therefore easy to understand that in exophthalmia, and especially when there is a constant retraction of the upper lid, the resistance to be overcome by the tarso-orbital portion and lachrymal bone crest portion of the orbicularis must become considerably greater.

A peculiar trembling of the lids not to be interpreted as Basedow's disease tremor, but rather as a tic has been observed by Scholer and Liebrecht (916) in a 68 year old man with severe Basedow's disease.

The lids exhibited an uninterrupted, rapid trembling which narrowed and widened the lid aperture without, thereby, fully closing it A portion of the cornea always remained exposed Strong pressure on the trunk of the nervous *infra* and *super orbitalis* of the facialis or upon its branches, ended the tremor of the lids at once, the upper lid was strongly retracted, so that a wide border of sclera came into view above the cornea and the eye took on the characteristic staring expression uninterrupted by any blinking This condition remained for a while, with pressure on the nerve trunk up to two *minutes, then the tremor of the lids* gradually began again During a transitory exacerbation of the disease symptoms the tremor of the lids also became greater

Liebrecht pointed out that Hermann (769) mentions a continuous rapid tremor of the lids in Basedow's disease But it was never possible for me to look into the case in the original so that I cannot decide whether it referred to a lid tremor of the same kind as in the case of Scholer Concerning a case of rapid intermittent vibration of the upper lids with nystagmus, see §105 below

§105. Tremor of the eyelids, or actual nystagmus, is an unusually rare manifestation in Basedow's disease.

One of Homén's (835) patients, a 30 year old woman, noticed occasionally a dancing back and forth of objects in a horizontal direction, whereby she had a feeling of trembling of the eyes. At the time of examination a nystagmus could not be discovered but only tremor of the closed lids (see above); but there is scarcely any doubt that the statements of the patient indicate a *nystagmus oscillatorius*, occurring occasionally. In the same year, Moutet (852) related the case history of a 27 year old female patient in whom, a *nystagmus oscillatorius* was observed together with severe general tremor, which was most pronounced in the extremities The patient had been treated for the same symptom in the hospital already a year before and discharged after decided improvement. The nystagmus was reduced but appeared again with the new illness in its earlier intensity. It is especially emphasized that

During excitement the trembling spread to the entire body. After an illness of four years the man was permanently cured.

It may also be pointed out here that the nystagmus in multiple sclerosis is distinguished from that of Basedow's disease by the following: 1 The oscillations occur considerably more slowly and 2, the nystagmus occurs only upon fixation, regardless of whether lines of vision remain parallel or converge; it is absent during involuntary unintentional gaze. Also, in that disease oscillations about the horizontal axis are observed.

There remain still two cases of nystagmus which are characterized by an eye tremor associated with signs which are also included in the symptom complex of Basedow's disease.

The case described by Bramwell (328) was a coal mine worker who, 18 months before the time of observation, had an attack of cardiac palpitation Later, profuse sweating upon the slightest exertion, and a visual disturbance caused by rapid illusory movements of the object developed. The nystagmus discovered at the examination has not been exactly described It seems, however, to have been an instance of the form of *nystagmus rotatorius* usual among miners. This was strongest with upward gaze The radial pulse was usually 72 beats per minute but every three or four days, without any evident cause, attacks of palpitation occurred in which the pulse rate rose and which ended in abundant sweat secretion At the same time, it was determined that the pupils were often unequal and the sweating sometimes remained confined to the left side Thyroid enlargement was absent During an especially serious attack, with a pulse count of 174, a slight protrusion and staring of the eyes and enlargement of the pupils was observed By taking a few deep breaths the patient could overcome the attack, the pulse, weak during the attack, fell to its usual frequency and became full again Amyl nitrite finally put an end to the attacks So far as the account allows of definite judgement, the rare condition of a stimulation of the *sympathicus* may have been involved.

Simeon Snell (737) gives an account of a case which was similar in many ways a 36 year old coal miner was suffering from pronounced coal miner's nystagmus Together with a rotary oscillation, a lateral oscillation also was present, and the eye tremor increased when the head assumed an oblique position Furthermore, a marked retraction of the upper lid and v Graefe's sign were found to be distinctly developed Exophthalmia, goiter, and cardiac signs were entirely absent S. Snell expressly added that, among the large number of cases of coalminers' nystagmus, this was the only one with such a complication

§106. One complication, tremor of the diaphragm is made evident by the type of breathing (P Marie 555, Charcot 613) A. Maude (1226a) stated that when, in rare cases, tremor attacks the respiratory muscles, a spasmodic laryngeal stridor can be produced which is audible at a distance

§107. Tremor and the other signs of Basedow's disease are not infrequently subject to a pronounced variation In attacks of tachycardia and cardiac palpitation the tremor can increase in intensity (Gerhardt 1105, L Jacobson 1739, Kocher 2197) (See also above §5) Even in the course of one day the strength of the tremor may vary How much it is influenced

(1222, p 135, no 31) tells among his 47 case histories of Basedow's disease. In the case of a 32 year old female, palpitation together with right-sided hemiplegia, goiter, and exophthalmia developed, at the time of the examination neither tachycardia nor protrusion of the eyes nor tremor of the extremities was present. But there was a continual trembling of the eyeballs in a vertical direction at about 150 oscillations per minute Upon attempted fixation all objects whirled about Furthermore, a considerable lessening of the sensitivity in the right half of the body was demonstrated In the right hand only the sensation for hot and cold objects remained Touch and taste were reduced on the right half of the tongue. The conclusion, that, in this case, the nystagmus was a symptom of the complicating hysteria can be drawn from the fact that in the eye peculiarities of the tremor which are characteristic of Basedow's disease were absent Also, this type of *nystagmus verticalis* is quite unusual

Hysterical nystagmus has been carefully studied only in recent times. L. Hirt (714), however, already in 1887, described a *nystagmus oscillatorius* occurring in the symptom complex of hysteria in a 22 year old woman, but no attempt was made to determine the rapidity or size of excursion of the trembling movements, which was the main question It is merely stated that voluntary movements were not impeded and that the rapidity and amplitude of the oscillations were not influenced either by the direction of gaze or by whether or not the patient knew she was being observed The eye tremor occurred first at the beginning of the malady.

One case of pronounced hysteria in a 17 year old female reported by Salerazis (1244) showed, together with a great trembling of the right upper extremity, a nystagmus of both eyes In the arm, the tremor was continual during standing as well as in sitting or lying position, and the oscillations occurred in rather large excursions four to five times a second Voluntary movements increased the number and size of the oscillations Writing was quite as impossible as was holding a glass of water without spilling the contents During sleep the hand remained still The nystagmus consisted of very rapid twitchings and occurred only at intervals The attacks lasted not longer than two minutes and appeared especially when an object was fixed or followed by the gaze or when a bright light fell upon the eye Closing the lids interrupted the eye tremor at once. The nystagmus and the tremor of the upper extremity occurred at the same time Both could be made to disappear completely by suggestion. The complete cure was interrupted by a relapse resulting from excitement

Borel (1942, p 247) reports a well defined case of hysteria in a 14 year old girl in whom a nystagmus of the left eye accompanied various other signs This was quite variable, sometimes *oscillatorious*, sometimes *rotarius*; it increased during the examination as soon as a bright light was shown into the eyes Its average speed amounted to two or three oscillations per second In the same eye, there was also paresis of the levator *palpebrae superioris*, combined with a spasm of the orbicularis. Under the influence of suggestive treatment the nystagmus as well as the ptosis disappeared, while a number of other symptoms continued Three and a half years later the left eye was involved by a nystagmus which continued for 14 days as a continual trembling in a horizontal direction.

A second case of nystagmus with hysteria, which Borel (p. 15) described, was that of a sturdy 21 year old watchmaker in whom a nystagmus of the left eye developed following a slight injury to this eye, in addition to whole series of severe hysterical symptoms. This consisted of oscillations, sometimes horizontal, sometimes rotating, and lasted for eight days At times it was combined with clonic lid spasms. Furthermore, there was a tremor of the left hand which, perceptible when at rest, increased considerably during voluntary movements and also showed in the handwriting

(2118) reports tremor was observed 13 times, 11 times in the hands only (65%) Among 16 pronounced cases of Jonesco (Balcscu 2145) the tremor was exhibited more or less clearly 13 times, several times only temporarily (81 25%) Among Kocher's (2197) 80 cases the tremor was never absent during the whole course of the disease In 76 cases the trembling was in the upper extremities, in 9 it was also in the legs and in 10 throughout the whole body Among 14 cases described by J A Hirschl (2192) some of them severe, the tremor was absent only once, that was in a severe case in a 16 year old boy. Among 170 cases of G R Murray (2553) in which attention was accorded to this symptom it was present in 163, sometimes to a very pronounced degree, in others only slightly, in a few cases it was only observed at intervals Tremor was therefore present in 95 88% of all the cases W V Holst (2385) never failed to find the characteristic tremor in his 34 patients with Basedow's disease Sometimes it affected the entire body Kroug (2700) has, to be sure, recorded the tremor only 86 times among his 106 cases, but from his observations in recent years he gained the impression that the records must have been incomplete, that tremor is scarcely ever absent, and that it occurs at least temporarily in all cases Of 50 patients with Basedow's disease under Riedel's observation (K Schultze 2749) 33 showed a more or less pronounced tremor Only in 2 out of 24 cases of Garre (H. Moses 2864) no tremor was found during the examination of the patients' condition R Stern (2991) never found the symptom absent among his numerous cases Also, in the 80 cases described by W Gilman Thompson (2772) the tremor was never absent, and the same was true of tachycardia, goiter, and nervous excitement Frank Billings (2806) reported the same concerning his 61 cases In a few, trembling was evident only during excitement Among my own 95 cases tremor was absent at the time of examination in 7 of them In 6 of these cases the symptom complex was otherwise incomplete also and in one the disease was already undergoing cure In 28 cases the tremor was strongly pronounced It was, therefore, observed in 92 65% of my cases

From the total of the statements described above the frequency of occurrence of tremor in Basedow's disease amounts to 99%

§109. O Mahler (775, p 339) first called attention to the fact that, while the patient is standing still, sitting or lying down, jerky backward and forward involuntary movements of the head or trunk or even of the extremities are observed in individual cases of Basedow's disease of the type in which tremor is distinctly developed, or only slightly indicated, or even absent These are distinguishable from typical *chorea minor* only by their smaller range of excursion When these movements follow one another very rapidly, as during mental excitement, or when the hands are stretched forward, they give the impression of a violent tremor Kahler designates these movement signs as choreatic tremor

He saw this sign exhibited to a very pronounced degree 4 times among 11 cases. Also, a case of von Strumpell's (1078 and 1918) may belong here, in which the tremor became so violent at times that cramplike twitchings occurred in the extremities and also in the facial muscles One case of F G Johnston (1120) was also similar a 45 year old man had such a violent tremor of the entire body that, at first glance, it

by mental excitement we have already mentioned above (§98). Ditisheim (1293) tells of a 20 year old woman in whom the trembling was stronger in the morning than in the evening. In a patient (female) of Kocher's (2197) the tremor also occurred in attacks when the patient was lying down—attacks sometimes so violent that they prevented her from sleeping.

Sometimes the trembling occurs only at intervals It may be absent at the time of the examination while the statement of the patient himself indicates that it has occurred previously; or it can be determined by a later examination when earlier absence of the tremor has been noted In one case which A Maude (1085) observed there had been goiter and exophthalmia for 20 years, the tremor was discovered only recently. The tremor may increase while other symptoms are diminishing; it can disappear during undiminished continuance of the other manifestations. A permanent disappearance of the tremor can, however, in general be looked upon as a favorable diagnostic sign.

§108. If we take into consideration also those cases in which tremor was certainly present at least during a certain part of the course of the disease, then statistical records compiled from pertinent publications, agreeing with my own experience, show that tremor is one of the most constant signs of Basedow's disease We believe we are justified with Charcot in taking it as the fourth among the cardinal signs.

P Marie (555) never failed to find the tremor among 15 cases observed in the saltpeter works, nor did O Kahler (775) among 7 carefully described cases A Lewin (777) noted trembling in 13 among 22 cases (59%), J. Russell (932) only rarely failed to find a more or less strong trembling among his 49 cases Among 14 cases of Cohen (1031), in which notations about the tremor are given it was absent in 3 (present in 78 5% of his cases) Hector Mackenzie (918 and 2205) never found the sign entirely absent in his approximately 40 cases Also, A Maude (1058) always found it in one stage or another of the malady Fr Muller (1134) missed the tremor in none of his 4 acute cases, described in detail The tremor was noted by Mannheim (1222) in all except 4 of his 47 cases (it was therefore present in 91 5% of his cases) Among 17 cases which Ditisheim (1293) reported from the Zurich Clinic, tremor is mentioned only 8 times It seems, however, that in early times this sign was accorded less attention, for after 1888 it was noted 7 times among 9 cases; 5 times it was extremely pronounced Passler (1362) found that among 51 carefully observed polyclinic patients with Basedow's disease, its characteristic tremor was present in 46 (thus in 90%) A case of irregular and less uniform tremor with more resemblance to alcoholic tremor, and another with an incomplete symptom complex and slower rhythm of the trembling motions are not included. Grandmaison (1578) stated that among the 32 cases studied by him the tremor was never absent. Among 18 cases from the Kast Clinic (Hunerfauth 1735) trembling of hands was always present, and the same was true among 18 cases observed by V. Mikulicz and Reinbach (2010). Among 24 cases of Krónlein, some of them mild (B Witmer 2034) the tremor was absent in only one case (thus it was present in 95 8%) Among 20 cases, which Schulz

(2118) reports tremor was observed 13 times, 11 times in the hands only (65%). Among 16 pronounced cases of Jonescu (Balescu 2145) the tremor was exhibited more or less clearly 13 times, several times only temporarily (81 25%). Among Kocher's (2197) 80 cases the tremor was never absent during the whole course of the disease. In 76 cases the trembling was in the upper extremities, in 9 it was also in the legs and in 10 throughout the whole body. Among 14 cases described by J A Hirschl (2192) some of them severe, the tremor was absent only once, that was in a severe case in a 16 year old boy. Among 170 cases of G R Murray (2553) in which attention was accorded to this symptom it was present in 163, sometimes to a very pronounced degree, in others only slightly, in a few cases it was only observed at intervals. Tremor was therefore present in 95 88% of all the cases. W. V Holst (2385) never failed to find the characteristic tremor in his 34 patients with Basedow's disease. Sometimes it affected the entire body. Kroug (2700) has, to be sure, recorded the tremor only 86 times among his 106 cases, but from his observations in recent years he gained the impression that the records must have been incomplete, that tremor is scarcely ever absent, and that it occurs at least temporarily in all cases. Of 50 patients with Basedow's disease under Riedel's observation (K Schultze 2749) 33 showed a more or less pronounced tremor. Only in 2 out of 21 cases of Garre (H Moses 2864) no tremor was found during the examination of the patients' condition. R Stern (2991) never found the symptom absent among his numerous cases. Also, in the 80 cases described by W Gilman Thompson (2772) the tremor was never absent, and the same was true of *tachycardia, goiter, and nervous excitement*. Frank Billings (2806) reported the same concerning his 61 cases. In a few, trembling was evident only during excitement. Among my own 95 cases tremor was absent at the time of examination in 7 of them. In 6 of these cases the symptom complex was otherwise incomplete also and in one the disease was already undergoing cure. In 28 cases the tremor was strongly pronounced. It was, therefore, observed in 92 65% of my cases.

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almost suggested chorea Buschan (1181, p 40) stated that he had seen this form of tremor and Perregaux (1233) also, in a young man In 5 cases of Murray (2213) a delicate vibrating tremor of the hands was combined with jerky irregular motions of greater amplitude G v Voss (2352) observed, in a 34 year old female patient, besides a delicate tremor of the hands, a choreatic shaking of the left leg, the oscillations were very considerable and occurred in irregular jerks A remark of Gowers (1106) that the tremor in many cases is so irregular that it suggests chorea, may perhaps refer to choreatic tremor I myself saw this phenomenon 3 times among my 95 cases, once in a 27 year old woman It disappeared, as did the tremor, after removal of the goiter on the right side In a 17 year old girl and a 21 year old woman choreatic twitches were evident in face and hands The latter patient had, at the age of 13, been treated for St Vitus Dance

Concerning complications with genuine chorea, see §116 below.

§110. In addition to tremor we also have to consider a series of disturbances affecting the motor functions A few, to be sure, seem to have only a loose relation to Basedow's disease or should be considered more or less unusual complications Others represent symptoms which are not unimportant but which are rather inconstant accessory signs of this disease.

Spasms

§111. Clonic spasms are a very rare occurrence among the motor disturbances.

Chvostek (332, No 42) reports a 48 year old female patient with Basedow's disease having hemiparesis of the upper and lower extremities and a paralysis-like weakness of the neck muscles Convulsive shaking occurred from time to time in the right shoulder and in the neck muscles In an 18 year old girl Gluzinski (468) observed, during attacks of violent cardiac palpitation, clonic spasms in both upper extremities and the right lower one together with contraction at the left knee joint Leube (1127) mentioned briefly, concerning one of his cases with pronounced Basedow's disease, jerking in all four extremities together with slight hypoglossus disturbances and difficulty in swallowing Kocher (2197), among his numerous cases, observed only quite isolated spasms in the finger

A 48 year old woman at the Leipsic Medical Clinic had typical signs of Basedow's disease, and clonic spasms occurred at longer or shorter intervals Chiefly the diaphragm, the abdominal musculature, the sternomastoid, and chest muscles were affected The upper leg muscles were sympathetically involved There also was conspicuous stiffness of the vertebral column About two weeks before admission, these painless but highly distressing jerks were experienced day and night After temporary remission, the convulsions began again to a greater degree, 16 days after entry to the hospital, the pulse became weaker Death followed during manifestations of collapse. The autopsy showed no visible changes in the nervous system

§112. Among 51 carefully observed polyclinic patients of Passler (1362), 8 complained of frequent cramps in the muscles of the calf of the leg In

2 cases painful cramps also occurred in the arms and hands. Hector Mackenzie (918) stated that according to his experience the occurrence of painful cramps in Basedow's disease is by no means rare Of 15 patients whom he asked about this, 13 stated that they had had such cramps and in one case the hands became stiff and the thumbs drawn inward during the attack. Sometimes hands were affected more frequently than legs and feet. The attacks occurred usually at night in bed One of his female patients had continued cramps in the hands (resembling tetany) and these kept returning for years A Maude (1226a and 1474), considered the occurrence of cramps or even tetany to be by no means rare in Basedow's disease In this assumption the two English authors stand in striking contradiction to the experience of other observers. It is, indeed, notable that few reports of tonic cramps and tetany in Basedow's disease are found in the pertinent literature. J. Faure (1305) describing a 40 year old female patient of Baylac, mentions painful cramps in the legs Once Joffroy (1117 and 1214) observed repeated attacks of tetany in the upper leg in the case of a Basedow's disease patient, a woman about 25 years old He mentioned incidentally that he had already seen such manifestations several times in Basedow's disease Kocher (2197) reported tonic cramps in only 3 among his numerous cases.

In the first one, a woman of 32 from a goiter area, experienced spasms in the neck Contractions with shooting radiating pains occurred frequently in both arms even during the early developmental stage of the malady These attacks later became more frequent, and usually occurred in the evening Tonic contractions followed clonic contractions and finally a tremor of the entire body developed

§113. In the two other patients the cramps had the character of tetany.

A woman of 35 (case 43) who came from a goiter region had a goiter on the right from her earliest youth Tonic cramps occurred in the developmental stage of Basedow's disease during her fifth pregnancy These still came and went even after delivery During the sixth pregnancy, and an exacerbation of the disease, the attacks became more frequent and more violent They decreased again after delivery The Trousseau sign as well as Chvostek's facialis phenomenon were present in typical form A violent attack of tetany was brought on by palpation of the goiter After two and one-half years the symptoms of Basedow's disease definitely improved However, tetany occurred every few weeks, always beginning and ending again in the left arm During these attacks tachycardia and cardiac palpitation were intensified She was favorably affected by thyroidectomy

A 22 year old unmarried female (case 71) developed without apparent cause signs of Basedow's disease general weakness, headache, sleeplessness, vomiting, diarrhoea, and enlargement of a small pre existing goiter The condition then remained for a time unchanged Only the exophthalmia increased and ulceration of the cornea occurred About four and a half years after the beginning of the disease, attacks of tetany occurred These lasted 30 seconds on the average, and affected chiefly the flexor muscles of fingers, hands and arms, less often of toes and feet. The calf muscles

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18 year old girl Here also, following administration of parathyroid, the tetany attacks were reduced and the symptoms also disappeared gradually

An interesting case of typical Basedow's disease with tetany is reported by Stumme (2888). The 26 year old patient, daughter of a phthisic mother, had a haemoptosis at the age of 16 Five years later a pea-sized lump appeared on the left thyroid lobe which increased steadily in size The right lobe likewise gradually increased in size Two years later the symptom complex of Basedow's disease was completed by cardiac palpitation, exophthalmia, tremor, sweating, and frequent watery diarrhoea Tapping the cheek, just beneath the anterior portion of the cheek bone, produced a distinct twitch of the corresponding corner of the mouth The sensory nerve trunks, especially the *ulnaris*, were equally responsive to pressure Since this extensive, soft, nodular goiter pushed the trachea toward the left, the right half of the goiter was surgically removed and a pea-sized goiter nodule connected with the left lobe was enucleated A rather insignificant exophthalmia remained Tapping of the facialis produced a suggestion of a twitch The girl had a fresh, healthy appearance and the pulmonary condition was arrested In the portion of the goiter removed by the operation a small epithelial body of usual size and reddish-yellow color was found loose in the capsule Microscopic examination of the center of this parathyroid gland showed an extensive tuberculous nodule with giant cells and epithelioid tubercules but no caseation

Logetschnikow (987) reported a 26 year old female with typical Basedow's disease A gray cataract had developed in each eye (see §77 above). Periodic violent tetany developed in the course of a few months

In three further cases of tetany in patients with Basedow's disease, other unusual complications existed

V. Jaksch (1045) demonstrated before the Society of German Doctors in Prague a patient with pronounced signs of Basedow's disease, a myxedema-like swelling of the lower extremities, and an increase in the susceptibility to mechanical stimulation in the facial nerve, as in tetany Gentle tapping over the branching area of the facial nerve produced a rather energetic contraction in the *risorius* and other facial muscles

E Dupré (1956) demonstrated a 34 year old female with Basedow's disease, suffering from sclerodermia and tetany Both parents were alcoholics She herself showed signs of degeneration (but none of hysteria) The first signs of Basedow's disease had developed when she was only 13 years old They were present in full at 24, when signs of scleroderma appeared At 29 years of age she had frequent tetany.

Latzko's (2093) 32 year old patient had suffered from osteomalacia since 1893 Three years later, at the beginning of her sixth pregnancy, Basedow's disease and typical tetany developed A slight improvement in the osteomalacia occurred under treatment with phosphorus, a well as a considerable improvement in the Basedow's disease No further tetany occurred since 1897. During the seventh pregnancy an exacerbation in the osteomalacia occurred (see §219 below)

From this review of the pertinent literature it is evident that tetany represents a very rare complication in Basedow's disease Recent investigations have shown it probable that the peculiar tendency of the nervous system of certain individuals to react to various stimuli by tetany depends on a functional disorder or insufficiency of the *glandulae parathyroidae*. In

were also involved There also were cramps of the tongue, larynx, osophagus and muscles of respiration

A female patient of 22 from the Erlanger Medical Clinic is reported by Mattieson (1471, p 50) Frequent painful tetany occurred in the flexor muscles of the fingers, left more than right. There was one episode of tetany of the left arm All these accompanied Basedow's disease after the goiter had become considerably smaller and harder, and the *bruit* and thrill could no longer be detected over the goiter. A surgical removal of a large part of the goiter resulted in an almost complete cure of Basedow's disease No more tetany occurred

In a case described by Steinlechner (1514), concerning a 20 year old woman, a slowly increasing enlargement of the thyroid gland had been developing steadily since about the age of ten One year before the patient was seized by painful cramps in both upper extremities, whereby the hands assumed the position typical of tetany. These cramps returned at two-day intervals Shortly afterward the patient, who had grown excitable and slept with terrible dreams, was attacked by violent cardiac palpitation and trembling of the hands A prominence of the eyes was noticed by those around her Also, a strong retraction of the upper lids was evident, but v. Graefe's sign was not distinguishable The tough, elastic goiter, over which a continual systolic *bruit* and thrill was discernible, caused an ever increasing dispnoea because of a compression of the windpipe Tracheotomy became necessary (see above, §30) In the further course of the disease the patient developed a purulent bronchitis and lobular pneumonia To this was added vomiting and profuse diarrhoea. Four weeks later death occurred following operation and with manifestations of complete collapse It should be noted that during the course of the observations frequent tetanylike spasms of the upper extremities occurred

The facialis sign was only slightly evident In regard to the finding of a pea-sized encysted *cysticercus* in the cortex of the *gyrus supramarginalis*, I would hesitate to attribute any special importance to it in the light of our present conception of the nature of tetany A foreign body in this region of the cerebral cortex or even a slight disturbance in the function of the parathyroids may suffice to release tetanic spasms

A 46 year old woman, reported by Loewenthal and Wiebrecht (2707), had a large neck even as a child. When she was 29 years old frequent stiffness of the hands became noticeable This ceased for several years, not appearing again until her thirty-seventh year when it occurred in an intensified degree after the death of a child At the same time the heart action became more and more rapid, reaching 165 beats a minute, so that at the age of 43 years a rightsided thyroid operation was resorted to Thereafter, the pulse rate was considerably reduced But one year later cardiac attacks occurred, the patient became more excitable, and contractions and a feeling of stiffness in the extremities came more and more frequently In her forty-sixth year the symptom complex of Basedow's disease was recognized (exophthalmia and lid signs were absent) and pronounced tetany was noted The Chvostek phenomenon was only indicated but the Trousseau sign was plainly developed The attacks lasted for hours and were especially noticeable in the upper extremities Since they became more and more frequent and more severe with speech or swallowing, parathyroid gland and thyroid substances were administered together Improvement began and became more evident after a few days when only the parathyroid was given Following the continued use of thyroid tablets, in which, it may be assumed, parathyroid substance was included, the tetany attacks became more and more rare, also, the tachycardia and the nervous symptoms improved and body weight increased

Marinesco (2540) observed a case of combined Basedow's disease and tetany in an

Bouchut's (280) case was a 13 year old girl. After two weeks the choreiform movements ceased while Basedow's disease continued for a while Gagnon (357 and 382) reports 2 similar cases The case of an 8 year old girl ended fatally after several years. A 12 year old girl with equally severe Basedow's disease recovered from the chorea after 2½ months while the disease continued in severest form A 13 year old girl had always been very delicate, Jacobs observed a *chorea minor* with almost uninterrupted motions combined with Basedow's disease Ulrich (2028) reported a 15 year old girl, poorly developed and delicately built, with an incomplete symptom complex of Basedow's disease and some symptoms of myxedema, choreiform movements also were displayed A 15 year old girl whom Zuber (2036) observed was subject to severe rheumatism of the joints with pericarditis and chorea in the course of a rather acute Basedow's disease The former disappeared quickly with a rapid improvement in the illness

Among 38 Basedow's disease cases reported by S West (686) one was complicated by a general chorea According to J Russell Reynolds (932) choreiform movements of the facial muscles, arms, hands, and legs are not unusual in this illness L Gior (155) tells of one case in which choreiform movements appeared at the same time as the disease involving muscles of the face, the neck and the upper and lower limbs Guéneau de Mussy (492) saw a combination of typical Basedow's disease with pronounced chorea in two cases (1362) Among 51 cases Passler (1362) found two in which choreiform movements began long before the disease appeared. In one case it lasted only a few weeks In a third case the first signs of goiter and exophthalmia appeared simultaneously one year before the appearance of a cardiac lesion In one case chorea seems to have been present for a long time (see below) In a case reported by Runge (2228), a 19 year old girl had no hereditary tendency Basedow's disease was followed in a few weeks by increasing restlessness associated with pronounced choreiform movements of the arms, legs, and head With a diminution of the general restlessness the chorea also improved, three weeks after its occurrence it had entirely disappeared K Rudinger (2339) presented to the Society for Internal Medicine in Vienna a 25 year old woman with acute Basedow's disease complicated by chorea Frank R Frey (2371) found juvenile chorea in its most highly developed form in the case of a 12 year boy with typical Basedow's disease

In the following cases the symptoms of Basedow's disease and chorea appeared simultaneously.

In the case of a 9 year old girl described by V Mathes (2541) trembling of hands and feet and lively choreiform twitching movements throughout the body developed after a violent fright Soon the child was attacked by violent cardiac palpitations, anxiety states, sleeplessness, excitation and irritability followed by the other signs of Basedow's disease This was the only case among 22 described by V Mathes in which choreiform movements were observed

In a few carefully observed cases chorea preceded Basedow's disease.

G A Sutherland (2349) studied 2 such cases One, a 26 year old woman, in whose family rheumatism and chorea had occurred several times, had recovered from an attack of febrile rheumatism at the age of 16 Six months later she developed chorea which lasted over a year This symptom did not return, but a tendency to cardiac

Basedow's disease, we can scarcely retain any doubt that increase or pathological alteration of the function of the thyroid gland is responsible. The existence of a closer relationship between the two diseases can perhaps be made more comprehensible when we remember that hyperthyroidism in itself carries with it a hypersensitivity of the nerves so that it only requires a relative insufficiency of the parathyroid bodies, perhaps caused by the pressure of the goiter, to produce the facialis phenomenon and the other indications of tetany. From this viewpoint, one would also understand that with the improvement or cure of Basedow's disease tetany, too, often disappears

Frankl-Hochwart[1] has pointed out a symptom complex which includes goiter, mechanical hyperirritability of the vasomotor nerves, and Chvostek's facialis phenomenon, while heart symptoms and tetany are lacking This trio is sometimes encountered in incompletely developed Basedow's disease

§114. Spastic torticollis was observed by G. W. Stern (2239) in the case of a 14 year old girl with Basedow's disease No abnormality of the cervical vertebrae could be discovered but a neuropathic tendency was probably present Contonnet (2364) tells of a 47 year old woman who was recovering from a violent emotional shock During improvement in the mental disturbance a moderate Basedow's disease and *torticollis spasmodicus* developed

§115. At this point a peculiar speech difficulty must be considered which Emmert (255, p. 219) had an opportunity to study in several patients with Basedow's disease in London. This was evident when the patients started to speak, opened their mouths fairly wide, and at the same time made cramplike movements of the lower jaw. Speech came only after a preliminary effort. In the case of one lady these movements were so violent that she could no longer swallow liquids Galvanic treatment brought about the disappearance of this symptom in a short time.

Chvostek (269, 14th and 15th observations) saw 2 cases, a male of 27 and a female of 55, with attacks of tetany which began whenever the patient attempted to take nourishment

Chorea

§116. Chorea or choreiform movements have been observed rather frequently in patients with Basedow's disease In a great majority of the cases it was this which indicated the already existing disease.

[1] *Die Tetanie der Erwachsenen* Wien, A. Hölder, 1907, p 78

The cases of Pelman (997) and Hay (976), both 68 year old females, show that patients with Basedow's disease can also develop chorea in an advanced period of life.

The first of these, a woman whose great-grandfather, grandfather and father, as well as an aunt on the father's side had chorea, had been ill since her fortieth year with typical Basedow's disease combined with a psychic disturbance. At the time of the examination she exhibited a general chorea with violent movements Increasing exhaustion and death followed Hay's patient, whose father had chorea at the age of 43, had herself developed chorea several years before This increased in three years until the woman was impeded in everything she did When she entered the hospital, signs of Basedow's disease were noted. It could not be determined whether these signs had existed before the development of the chorea. Here, also, exhaustion and death followed

An 18 year old female patient of Kelly (410) suffered from Basedow's disease, pronounced hysteria, and choreiform movements of the arm which may probably be counted as one of the signs of the hysteria

Of the cases described all were females except the one (of Bootz) in which the symptoms of Basedow's disease occurred a long time after the chorea. Six patients were children (between 8 and 15 years old). Two cases of so-called *chorea senilis* were notable because of a conspicuous hereditary *predisposition A neuropathic inheritance was indicated in a few other* cases. Several times it is particularly emphasized that it affected delicate, sensitive individuals In several cases the Basedow's disease was especially severe, as in the two cases of Gagnon, those of Pelman and Hay, and those in which the chorea with unusually violent movements preceded a hemiplegia or was added to it, as in the cases of Clarke, Bradshaw and Dinkler.

Factors favorable to the appearance of chorea included mental excitement, fright, pregnancy, or polyarthritis with endocarditis Among these states we shall see that Basedow's disease plays an important part in the etiology Furthermore, this cause has been recognized in only a few of the case histories contributed In Zuber's case (see above) acute arthritis began during the course of the Basedow's disease It was followed by chorea Bradshaw attributed the systolic sound at the base of the heart to a *vitium cordis* and traced the hemiplegia to a cerebral embolism (see above). He gives no evidence for this assumption and the case history emphasizes especially that the patient had never suffered from rheumatism.

In the cases in which chorea preceded Basedow's disease by a more or less lengthy period (see above) it probably is a matter of a more or less changed combination in one and the same individual In those cases in which the chorea arose during the course of the disease and disappeared while the latter continued, or where it arose simultaneously with the outbreak of the disease signs (in a case of Passler and that of Mathes), or a

palpitation, slight trembling of the limbs, and nervousness remained During the final year the signs had increased and a pulsating swelling had developed in the neck. Soon afterwards all the usual signs of a typical Basedow's disease were plainly evident Choreiform movements were no longer observed. A 15 year old girl, otherwise healthy, had attacks of chorea which recurred at long intervals A sister had suffered from Basedow's disease since her sixteenth year The last and seventh attack occurred one year previous to the disease and lasted quite a long time, leaving her with a *weakness of the right arm and leg Simultaneous with the last attack the* thyroid gland became enlarged and the eyes assumed a staring expression. Exophthalmia and v Graefe's sign were not present One year later, however, all the signs of pronounced Basedow's disease appeared in rapid sequence Pulsation appeared in the still further enlarged thyroid gland Besides slight choreiform twitching in the limbs of the right side, there was a typical tremor of the arms, legs and tongue. Frank R Frey (2374) reported a patient with pronounced tremor and chorea followed *by all signs of Basedow's disease.*

A 14 year old girl was a patient of Passler (1362, p 222) The choreiform movements were said to have been present for 7 years Finally, signs appeared which were attributable to Basedow's disease Bootz (694) told of a 14 year old boy who had suffered from chorea at the age of 5 Also, two of his siblings had had chorea at various times He seems to have had a goiter for a long time Only after his twelfth year did *the first signs of Basedow's disease appear and develop fully* In a case of Rockwell (50) choreiform movements had occurred since childhood and were initiated by hysteroepileptic attacks At the age of 24 cardiac palpitations were followed by the other signs of Basedow's disease

In rare cases the chorea remains confined to one half of the body during its entire course or for a while This happened in 3 cases in which the chorea was added to a severe Basedow's disease complicated by cerebral disorder.

Clarke (818) tells of a woman aged 30 with severe Basedow's disease After 2 years, severe nervous irritability and left-sided paresis also developed Five and a half months later choreiform movements occurred in almost all the muscles, together with an increase of the paralysis of the left side. Violent attacks of mania, a rapid loss of strength, and death followed

A 23 year old woman whom Bradshaw (951) observed had suffered from Basedow's disease for four years After this disease had lasted six months a rightsided chorea occurred and one and one-half years later the patient suffered a right hemiplegia At the time of the demonstration chorea on *the left* was so severe that *the patient* was unable to carry food to the mouth During sleep choreiform movements ceased. It should also be noted that a systolic murmur could be heard at the base of the heart

Drinkler's interesting case (1711 and 1954) was a 42 year old woman During a severe relapse of Basedow's disease the cerebral symptoms with choreiform twitching began in the extremities on the right and in the face, but soon extended to both sides. This was so severe at times that the patient had to be fed Since the tongue was affected by a rapid twitch she was unable to make herself understood After a left hemiparesis in the further course of the disease twitchings were limited more and more to the right.

A 36 year old female patient, with poor heredity, whose case history Cohen (1031) described, had a first epileptic attack at 19 At 33 the first signs of Basedow's disease appeared and gradually developed completely. A female patient of Kowalewski (842) with very poor heredity had attacks of epilepsy at nineteen, about one year after marriage The attacks followed one another at long intervals At the age of 24 episodes of absentmindedness occurred which lasted from half an hour to several hours After the age of 32 these attacks of absentmindedness lasted longer, from 8 to 18 hours, and were accompanied by mania At 40, attacks of cardiac palpitation occurred These became violent and continuous Two years later exophthalmia, goiter, etc developed During the development and duration of Basedow's disease epileptic attacks and mania persisted, occurring two to three times a year During these episodes the symptoms of Basedow's disease always became worse Thereafter, various signs of myxedema developed (see §221 below) A 37 year old female reported by Joffroy and Achard (1119) had epileptic attacks since she was 28 and Basedow's disease after her thirty-third year Death occurred during *status epilepticus* The evidence of syringomyelia and an angioma in the posterior cranial fossa was found The case described by Mannheim (1222, p. 133) was a 32 year old female who, at the age of 26, had epileptic attacks following a difficult delivery These attacks were most violent when menses did not occur Five years later, after a violent fright, very pronounced Basedow's disease gradually developed In the case of a young man described by Gildemeester (136 and 153), epileptic attacks preceded Basedow's disease by several years After the development of the latter the attacks disappeared and did not appear again A young man whom Ballet (535, obs 1) observed had epileptic attacks for a number of years Under bromide treatment they ceased but were followed, at intervals of 8 to 14 days, by slight twitchings in the tongue without the loss of consciousness which previously preceded the attacks In the meantime the symptoms of Basedow's disease developed gradually A 21 year old sturdy but nervous man under Bonet's (1695) observation had suffered from a mild form of epilepsy for six years After three years Basedow's disease developed A case of P Gros (591) had epilepsy before developing Basedow's disease Concerning a 20 year girl, Fink (179) mentions only that before the outbreak of Basedow's disease she had suffered from spasms of an eclamptic and epileptic nature A 40 year old female patient with Basedow's disease, observed by Panas (496) had epileptic attacks from her eighth to eighteenth year In her thirtieth year she showed the first symptom of the illness One of my patients, a 29 year old female worker, had previously had five or six typical epileptic attacks weekly At the time of observation the seizures occurred only during excitement, she struck out about her, jerked about, and was unconscious for about fifteen minutes

§119. *In several cases the interval between the first occurrence of the* epileptic attacks and that of Basedow's disease was brief

Such a case is described by C H Parry (8), a 50 year old female, soon after the beginning of a severe epilepsy with a succession of over 500 attacks, developed a swelling of the thyroid gland, powerful carotid pulsations and an increase in the pulse rate to 96 beats a minute J B Nias (1063) describes the case history of a 33 year old workman, previously healthy, who suddenly suffered a severe attack of epilepsy without known cause. Then followed a few more mild attacks of dizziness and confusion without loss of consciousness; two weeks after the first attack the eyes assumed a staring expression Furthermore, the dizzy spells did not return The patient still

few weeks later (Runge, Rudinger), or finally, in cases like that observed by Sutherland, in which the initial symptoms of Basedow's disease first developed at the cessation of a protracted chorea, I do not wish to attribute as much importance to the change as Mobius (1476, p 53) When one considers the many transitions which lead from a general unrest, so frequently observed in patients with Basedow's disease, and their tendency to be in constant motion (see §149), passing from this stage to the intermediate of oft-repeated, slight choreatic twitching and then to choreatic movements and typical *chorea minor*, one cannot avoid the conclusion that the damage caused by Basedow's disease (see Pathogenesis) is likely to produce chorea also. In the cases complicated by hemiplegia, signs of cerebral motor stimulation precede the manifestations of paralysis.

Epilepsy

§117. In a number of cases Basedow's disease and epilepsy are found in one and the same individual

Epileptic or epileptiform attacks were noted by S West (686) once among 38 cases, by J Russell Reynolds (932) once among 49, by Cohen (1031) 3 times among 16, and by Mannheim (1222) once among 47 cases I, myself, have observed, among 95 patients with Basedow's disease (see below) one case which belongs in this category Severe cases of epilepsy occurred, therefore, among 245 cases of Basedow's disease at a rate of 3% The group is too small, however, to permit definite conclusions regarding the frequency of this combination

§118. The relationship of the two diseases to each other is rather varied In the majority of cases the patients suffered from epileptic attacks for a shorter or longer period before the appearance of Basedow's disease

In the case of a girl described by Taylor (59) epileptic attacks had occurred since childhood With puberty they gradually ceased and soon afterward the symptoms
o
o
disappeared [illegible]
speech difficulty with paralysis of the tongue arose, lasting several days, with increasingly severe headaches and signs of Basedow's disease A 55 year old patient from Mendel's polyclinic, reported by Kogel (1333), had epileptic attacks said to be the result of a fright since he was nine years old In the last five years these became less frequent A swelling in the neck became evident During the fifty-second year these attacks disappeared entirely while symptoms of Basedow's disease developed to a more and more pronounced degree Among Oliver's (783) cases the first epileptic attack in one of them, slight at first, appeared at the age of eight, later more severe attacks occurred, and at 14 the signs of Basedow's disease appeared A 45 year old patient of Benedict (348, observation 355) had epileptic attacks since childhood. During recovery from typhoid fever eight weeks previous to admission, tremor, cardiac palpitation, a goiter of considerable size, and a strong protrusion of the eyes developed.

year. For several months a typical epilepsy was added to this, sometimes with three seizures in a day, sometimes free intervals of up to two months. The case observed by Ballet (obs V), the 19 year old daughter of an habitual drinker, had a swelling observed in the neck for two years Since that time the classical pattern of Basedow's disease had developed Four months after the appearance of the first definite sign of this disease the first epileptic attack occurred and in the same night two more followed. A year later a series of attacks again occurred The Basedow's disease continued unchanged in the meantime A 27 year old woman observed by Merklen (491) had epileptiform attacks with twitching of the face and extremities during an acute exacerbation of the Basedow's disease which had been present for six years Sometimes the attacks were mild, sometimes severe, sometimes occurring suddenly in the middle of a conversation At the end of the seizures conversation was resumed where it had left off The attacks were preceded by an interruption in the heart beats for up to five seconds. Bristow's 25 year patient (646) with Basedow's disease complicated by bilateral *ophthalmoplegia exterior* had paresis of cranial nerve VII and the motor root of the Vth and a right-sided hemianasthesia (see §127 below), epileptic attacks also occurred at intervals of two to three weeks.

The simultaneous occurrence of epilepsy and Basedow's disease was also mentioned by Passler (1362, p 212) He stated that two sons of an alcoholic suffered from this disease and one from epilepsy also. Gerard-Marchand (Herbert 1973, p 159) spoke of an 18 year old girl in whom an operation upon the *sympathicus* had affected the epilepsy very favorably but the Basedow's disease only slightly.

§122. Although such simultaneous occurrence must be looked upon as accidental even in many cases in which epilepsy and Basedow's disease occur in the same individual, still, a careful analysis of the various cases points to a series of circumstances which indicate a closer relationship between the two diseases. Also, we may find in the simple fact of their simultaneous occurrence an indication of a neuropathic a *parente morbide* (neuropathic etiology) of these two diseases (Ballet 535, Boinet 1695). We find also however, in a number of patients afflicted with Basedow's disease, that epilepsy is present in parents and siblings Important for the relationship of the two diseases to one another are, it seems to me, the cases of simultaneous or almost simultaneous occurrence of the two diseases (see §120 above) as well as those in which the epileptic attacks began during the course of Basedow's disease (§121) Especially Merklen's case of sudden, acute exacerbation of Basedow's disease which had been present for years, and Chevalier's most acute case, which fell within the pattern of a severe intoxication, give the impression throughout that the epileptic attacks are produced by the same poisons Pointing also in the same direction is the disappearance of the epileptic attacks simultaneously with the remission of the Basedow signs (Nias) or acute symptoms (Merklen)

The frequent absence of epileptic attacks after the beginning of Basedow's disease is noteworthy. This occurred in the cases of Taylor, Cohen, Kogel, Mannheim, Gildemeester, and in an observation of Ballet (obs. I). In a case of Raynaud the epileptic attacks became less frequent upon the

had the sensation as if something were about to happen to him several times At that time a certain degree of aphasia began. In the meantime exophthalmia and lid signs became more and more evident Three weeks later the signs involving the lids subsided, after two weeks the patient was cured and free from distinguishable goiter or palpitations

§120. An observation of Jonnescu (described by Balacescu 2144, p. 97) illustrates the transition to cases in which epilepsy and Basedow's disease occurred simultaneously.

A 17 year old female patient of Jonnescu, following a fright three years before, developed epileptic attacks with jerking of the extremities but without loss of consciousness These recurred every two or three months Since that time the patient experienced cardiac palpitation during any excitement After two and one half years a swelling on the neck was observed A year later she had a typical epileptic attack and the signs of Basedow's disease developed more and more clearly. Only exophthalmia remained absent during the entire course. A woman of 25 reported by Raynaud (338) suffered an epileptic attack when she was 20 years old, following a severe fright Since onset, the attacks recurred every two or three days, later two or three times a month. At about the same time symptoms of Basedow's disease appeared With the onset of tremor epileptic attacks became less frequent A 24 year old female patient of S West (686) developed epilepsy at the age of 22 The attacks occurred every two weeks and lasted about one hour After the first attack she suffered from cardiac palpitation, shortness of breath, profuse sweating, and prominence of the eyes A year later a swelling of the thyroid gland was also discovered.

In the case of a 26 year old female patient of Delasiauve (299) the first epileptic attack appeared without any known cause At first the attacks were quite frequent, later less so At the same time and concurrent with them, the symptoms of Basedow's disease developed in very typical manner. A case under the observation of Unna (reported by Berliner 1104), a 21 year old woman whose sister suffered from epilepsy, developed rightsided hemicrania, epileptic seizures, and the signs of Basedow's disease together with loss of hair immediately after she had, it was said, undergone a criminal attack. In a case described by Chevalier (882) the disease took a very acute course The patient was a 30 year old man, healthy up to that time and with no hereditary predisposition A few days after a change in his personality and mood, a symptom complex of severe Basedow's disease occurred The first epileptic attack appeared at this time A few days later two new attacks followed and on the next day death occurred during repeated seizures

§121. In some cases, epileptic attacks begin during the course of Basedow's disease.

Cohen (1031) tells of a 32 year old woman who had suffered from cardiac palpitation since she was 16 and from tremor of the hands for six years. For six years she had daily epileptic attacks After an especially violent attack a year later, she suffered a leftsided hemiplegia which continued for two years. Meanwhile the symptom complex of Basedow's disease became more and more complete and seemed fully developed. The epilepsy continued with daily attacks.

In the case of a 20 year old washerwoman who was under observation by Ballet (535, obs II) fully developed Basedow's disease had been present for more than a

hysterical symptoms were also present. Among Pässler's (1362) 51 cases the symptom appeared 10 times In 11 among 180 patients with Basedow's disease reported by Murray (2553) weakness in the legs was the only complaint; in 7 the legs bent slightly; 5 fell down and were unable to walk One of these could not get up again without [illegible]

several of my cases

Earlier observers mentioned a paralysis-like weakness and a bending of the legs, para-pareses and paraplegia, in isolated cases; for example Aran (78), Warburgton Begbie (109), Sutton (410), Saint Marie (736) and Vigouroux (740). Later, the attention of many observers was directed to these symptoms. The cases of De Ranse (675), Suckling (1153) and Nonne (1628) were referred to as paraplegia.

In several cases of Basedow's disease with paraplegia unquestionable symptoms of hysteria were present Under such circumstances it is always *rather difficult to determine to what extent the paraplegia is to be considered* as resulting from Basedow's disease and from hysteria.

Charcot (816 and 817) reported in 1889 a patient who, besides showing the classical signs of Basedow's disease suffered from considerable emaciation of the legs. The response to electric stimulation was unaltered He emphasized that under *electrical treatment the signs of Basedow's disease improved and the signs of hysteria* developed progressively

Ballet (535, obs VII) contributed the case history of a 31 year old female patient of Teissier fils In the course of Basedow's disease which she had for four years, pain suddenly occurred first in one leg, then in the other, and a paraplegia followed, such that the patient could not stand or walk alone The legs remained stiff *Sensitivity was retained or even increased* This was also *accompanied by various signs* of a hysterical neurosis.

A 30 year old female patient reported by O Kahler (775) in detail had signs of rather severe Basedow's disease which developed so rapidly that she was soon bedridden A marked pulsation of the abdominal aorta (see above §15) caused the patient to keep the legs always drawn up against the body In this position a contracture gradually developed After one year, when the general condition had improved and the abdominal pulsation had disappeared, it appeared that, beside an incurable contracture at all joints and an extreme emaciation which had taken place in the lower extremities, a paraplegia also had developed The sensitivity was not affected and the reaction to electric stimulation at least not notable The knee jerks were absent Kahler was inclined to look upon this paraplegia as hysterical and pointed out that many times before, muscle contractures had been observed during long-continued hysterical paraplegia

Joffroy (1117) several times has observed paraplegia during Basedow's disease The condition sometimes called to mind the ataxia of tabes patients Chevallié (489) tells of a 22 year old female Basedow patient with paraplegia and ataxia With the improvement in the acute attack of Basedow's disease the ataxia disappeared little by little, together with the paralysis of the legs In the case of a 25 year old *female reported by Mannheim (1222)*, the right leg was "as if paralyzed" and was

onset of tremor A few times an exacerbation of the signs of Basedow's disease were observed during the epileptic seizures As in the case of Kowaleski (see above) and in two cases of Ballet: the cardiac palpitation became stronger, the swelling of the thyroid gland increased and became painful One must, however, not overlook the fact, that the circulatory disorder following tonic and clonic spasms during the attack can be held at least partly responsible for it.

Whether, indeed, in certain cases the seizures designated as epileptic or of an epileptic nature were hysterical by nature cannot be clearly decided on the basis of the reports. Furthermore, sometimes the absence of signs of hysteria is especially emphasized.

Paralysis-like Conditions and Paraplegia

§123. More frequently paralysis-like conditions, pareses, or paralysis have been observed in Basedow's disease In part, at least, they are directly dependent upon it, or are, in fact, to be considered as belonging to the disease itself

§124. In pronounced cases of Basedow's disease a sign often develops which is characterized by a sudden weakening of the legs, as if they refuse to function. The patients are momentarily unable to walk any farther. In a higher degree of the ailment it causes a buckling of the legs. It can happen that the patients fall, full length, unless they can hold on to something, although they do not have any feeling of dizziness. Getting up again without aid is difficult or impossible for them The disturbance passes after awhile but it may recur at uncertain intervals. It is this latter manifestation to which Charcot (816 and 817) first called attention as an inconstant and not very frequent sign of Basedow's disease which he described as *l'effondrement des jambes* In England it is known under the descriptive name of "giving way of the legs" In severe cases the weakness of the legs increases still more, and becomes a paraparesis or paraplegia. This form of paralysis is a relaxation accompanied neither by pain nor by a disturbance of the sensitivity. The bladder function remains intact, response to electric stimulation unaltered The knee reflexes are reduced or entirely absent With improvement in the disease symptoms, the paralysis may disappear again completely It can probably be distinguished as a rule from hysterical as well as from spinal paraplegia by the characteristics just described.

Buckling and paralysis-like weakness of the legs has been observed by H. MacKenzie (918) in 12 among more than 30 cases Among 47 cases of Mannheim's (1222) this phenomenon was noted 8 times, always in women In one case, unmistakable

variety of diseases. He determined which weight could just be lifted by each group. A patient with Basedow's disease, taken as an example, showed the following results:

	right	left	Normal woman of same age right	left
Shoulder adduction	3.8	3 6	13	12
Shoulder abduction	1.9	1 5	15	12
Elbow flexion	4.8	4.0	30	25
Elbow extension	5 6	4 8	18	14
Finger flexion	6 5	5 5	20	18
Hipjoint flexion	4 6	4 1	30	30
Hipjoint extension	5 1	4 6	35	35
Hipjoint adduction	3 5	4 5	15	15
Hipjoint abduction	4 0	4.0	15	15
Knee bending	7 1	6 6	30	30
Knee extension	13.4	12 1	40	40

Impairment of muscle strength as well as abnormal fatigue improve perceptibly with improvement and disappearance of the other symptoms of Basedow's disease.

Whether this muscular weakness is dependent upon a disturbance of the innervation, or whether we must look upon it as the result of a general metabolic disturbance (see §233 below), or as the expression of a local diseased state of the striated musculature (see Pathological anatomy of Basedow's disease), is not easy to determine The first possibility may be considered This is shown by actual transitions to real paresis and paralysis, according to P. Londe (1878) this relaxation of the muscles is evident in many cases, especially in the flabby facial expression and overstretching of the leg muscles

§126. Mention should be made here of a sign upon which Joffroy first centered attention the lack of contraction of *m frontalis* when the eyes turn upward and the lids are raised This is therefore called the Joffroy sign Up to now generally little attention has been expended on it J H. Abram (2142) stated that he had observed it only once among 5 cases, within two years I, myself, have met with it 7 times among the 22 patients where I paid attention to it Among 50 persons chosen at random whom I have tested for this manifestation, the forehead wrinkling was very definite 42 times, only slightly indicated 8 times, and never entirely absent DeBove (1836) was impressed by the unusually smooth brow of a 39 year old woman patient, as if the *m. frontalis* were paralyzed with an acute Basedow's disease She could, however, wrinkle the forehead voluntarily and the muscles reacted promptly to electrical current. But with upward gaze the forehead remained smooth.

dragged in walking In the right foot there was a tingling sensation About the subsequent course nothing is mentioned (Concerning complications with tabes, see below, §144)

In this connection those cases should be *recalled in which the manifestations of* astasia-abasia in patients with Basedow's disease were observed, that is, the inability to stand or to walk with unhindered backward movement of the legs even when muscular energy, coordination, and sensitivity are fully retained. In the majority of these cases it seems to have to do with a complication of hysteria, as in an 18 year old girl patient of Eulenburg (888), in whom the symptom was made to disappear by suggestion. Similar cases were a 32 year old female patient of Dienot (1700) and others Renault (931) tells of a 17 year old girl from the saltpeter works in whom typical abasia was associated with signs of Basedow's disease At every step she took, a flexion of the knee occurred as if someone had given her a blow in the hollow of the knee joint The right leg was more affected than the left and bent more frequently Sometimes both legs bent at the same time causing the patient to fall on the floor. Before the appearance of this symptom she had very painful cramps in the feet and lower leg in attacks lasting about 5 minutes and recurring frequently With the development of the abasia the cramps disappeared No signs of hysteria were present at any time

In a case of Maude (1057), that of a 45 year old woman, an astasia-abasia arose during the recovery from a left-sided ophthalmoplegia exterior and from a facial paresis which had accompanied the Basedow's disease

§125. Often patients with Basedow's disease complain of profound muscular weakness noticed especially in the use of the arms and legs. Frequently this feeling of weakness is accompanied by a general emaciation. But it may also happen that patients in spite of considerable emaciation do not complain of the feeling of weakness, while others suffer from great weakness without being very much emaciated A feeling of fatigue and weakness, especially in the legs, is sometimes present even though other disease signs have not yet attracted attention. The feeling of fatigue is usually more pronounced upon getting up in the morning.

hands or sit up in bed Knee jerks were greatly diminished and the patient gave the *impression of being a paraplegic But with improvement in her general condition* the patient again gained strength In the case of a 40 year old patient of Kocher (2197) there was an unusual weakness of the neck muscles such that she could not hold her head upright. Chvostek (332) has seen a similar state in the case of a 48 year old man.

Fr. Muller (2718) was often impressed by the slight muscular strength and rapid fatigue of patients with Basedow's disease. He tried to compute the muscle energy more exactly by a system of measurements. He had weights lifted by means of a simple roller apparatus, and brought into play the most important functionally connected groups of muscles of healthy persons of both sexes and various ages and of those with a great

accommodation were retained as well as a normal visual acuity The forehead could be wrinkled cross-wise and up and down, although the lower facialis branches were paralysed. There was a marked reduction in response to electrical stimulation in the region of the facialis nerve. The chewing muscles seemed weakened There was a paralysis of the soft palate and muscles of the shoulder girdle, and a distinct atrophy of the right pectoralis muscle

Of special interest is the subsidence of the original left oculomotor paralysis concomitantly with the development of an associated visual paralysis The damage seemed to have affected only the supranuclear centers or cortical tracts. Retention of the reflex eye movements upon change in position of the head showed that these centers mediated an impulse passing from the labyrinth through the *nervus vestibularis* in normal manner

I believe that we must regard the bilateral ophthalmoplegia exterior in Basedow's disease as a more or less *completely associated visual paralysis*

A further case of complete *ophthalmoplegia exterior bilateralis* was observed by Chevalier (882) in an acute fatal case of Basedow's disease *Together with the usual signs a paralysis developed in the case of a 30 year old man with no hereditary trait* The eyes remained immovable, looking straight forward The lid apertures gaped widely, and the eyes could not be completely closed Furthermore, there was a *paresis of the facialis on both sides such that the face assumed a mask like appearance* The speech became nasal, sometimes unintelligible The tongue movement seemed disordered The sensation remained normal throughout

Liebrecht (916) reported 2 cases *of Basedow's disease from Schoeler's Clinic* each distinguished by the presence of a bilateral *ophthalmoplegia exterioris* A 68 year old man and a 58 year old woman had a complete paralysis of lateral and upward eye movement Downward gaze was limited to a slight degree in the case of the man but not noticeably disturbed in the case of the woman Nothing was mentioned concerning the condition in the upper lids There seems to have been no ptosis in the two cases, in the first case, with moderate exophthalmia, the cornea of the right eye was *covered with a yellowish, dry, scaly mass (see §55 above) such as occurs when the* purulent, infiltrated cornea is insufficiently covered and is subjected to drying in the second case there was an abnormally wide palpebral fissure and a von Graefe's sign

Joffroy (1117) mentioned a case of Basedow's disease with *ophthalmoplegia exterior* but without ptosis, for 5 years Improvement followed electrical treatment over the eyes Signs of hysteria were not present

Suckling (1152) made the brief remark, in telling of other cases, that he had seen a patient with Basedow's disease and bilateral ophthalmoplegia *exterior* He considered the disorder a functional one which attacks mainly young females A ptosis of the upper lids was not expressly mentioned, but may have been present

A Gordon (2190) reports a middle aged woman who experienced a bilateral paralysis of the levators of the eye On the following day lateral movement was also *restricted A few weeks later a protrusion of both eyes was noticed* A week later came swelling of the neck, cardiac palpitation, a rapid pulse and trembling of the hands Soon the oculomotor paralysis became complete and the light reflex of the left pupil became sluggish

Ophthalmoplegia and Bulbar Paralysis

§127. The ophthalmoplegic and bulbar paralysis signs arising in isolated, mostly severe cases of Basedow's disease are of special interest. Sometimes only the former are present and sometimes only the latter, sometimes they occur in combination. This process follows the pattern of a polioencephalitis or poliomyencephalitis Notable are the cases of bilateral *ophthalmoplegia exterior* Usually they pursue their course without ptosis, more rarely with it

The very instructive case in this connection was observed by Fr Warner (533 and 2032) and Bristow (646) A female of 25 had Basedow's disease for four years, with a picture of *ophthalmoplegia exterior bilateralis* and bilateral ptosis Limitations of movement were more pronounced in a horizontal direction than in a vertical one Furthermore a paresis of the vii cranial nerve and the motor root of the vth was determined The patient showed, beside the major signs of Basedow's disease, great irritability, frequent vomiting and violent tremor of the legs The paralysis appeared when the goiter was in the process of reduction As Bristow reported 4 years later, there were added, in the further course of the disease, a rightsided hemianaesthesia, color blindness ipselateral loss of taste and smell, paralysis and stiffness in the right arm and leg, epileptic seizures and finally death from acute bronchitis two years after the eye-muscle paralysis No signs of syphilis were present and Bristow also believed that hysteria could be excluded in view of the uniform progress of the changes without alteration of the paralysis At autopsy (macroscopic) no changes in the brain were found A similar if less severe case was a female of 43 reported by Fr Warner, (2032) in 1900 The illness began 10 years earlier with a diarrhoea lasting nine months Four years later, a general weakness and all the signs of Basedow's disease developed Two years earlier she had a partial loss of limb power for walking although the goiter was growing smaller At the time of final observation in 1899, no goiter could be found any longer There was marked limitation in the movement of both eyes, but not equally in all directions and not to the same degree in both eyes There was no complaint of double images During the period of the observation no noticeable alteration occurred There was no evidence of syphilis The question about the indications of hysteria was not decided

In the interesting case of Jendrassik signs of paralysis and the first signs of Basedow's disease appeared at almost the same time A 16 year old male with no hereditary trait had worked three and half years in a cloth factory where a lead dye was used A diplopia occurred, associated with signs of a left oculomotor paralysis One month later chewing and swallowing became difficult He could not whistle or talk continuously and sometimes had a dry cough. As these manifestations gradually improved over an interval of about two weeks, the symptom complex of Basedow's disease became complete The left ptosis became a minor weakness of the

right one, [illegible]
sometimes upward, although for weeks there was only a minimal motility Involuntary eye movements corresponding to changes in position of the body were well executed, and were easily observed on the protruding eye. The pupil movements and

degree of insufficiency of convergence which we have learned to recognize as a sign, although not a frequent one, of Basedow's disease.

A 67 year old female reported by Liebrecht (986) had good muscle balance for distance. For the 25 cm range under a prism, with the eye turned upward, an insufficiency of convergence was compensated by an abducing prism of 16° When the prisms were removed no fusion movements were executed In order to bring the crossed double images together an abducing prism of 16° was again needed From this the author believed he could assume a convergence paralysis Since a prism of 16° represents a lateral turn of the eye of about a two meter angle, the insufficiency of convergence can not be regarded as of very high degree in the case of an old woman who had already lost her accommodation ability entirely.

In the case of an anemic 22 year old girl noted by Vossius (1387) for an incomplete symptom complex of Basedow's disease the lateral eye movements were entirely normal, convergence was "almost entirely impossible" and remained so even after the general condition and other symptoms of the disease had improved Schmidt-Rimpler (1786, p 377) mentioned, without stating further details, that he had seen one case of real convergence paralysis in Basedow's disease.

Paralysis of single eye muscles or groups of them, in one or both eyes, in different combinations have been encountered in quite a number of cases but are, nevertheless, in general, rare in Basedow's disease. In those cases of which a fairly exact description is available, the disorder of a nucleus or tract can be accepted with moderate probability Perhaps this assumption may be extended to other cases in which a chance complication is not found

To v Stellwag's case, in which a bilateral *abducens* paralysis appeared during the course of the disease, reference has been made already above (p 185). *Abducens* paralysis was also observed by Eulenburg (334) in 1 case, and then by Liebrecht (916) in the case of a 55 year old woman The paresis was rightsided and developed after the Basedow's disease had existed for 18 months A paresis of the left *abducens* was mentioned by Cohen (1031) in the case of a 26 year old woman, and by Hock (1323) in that of an 8 year old girl Mobius (1478 p 29) saw an *abducens* paralysis in the case of a man who was probably syphilitic but who had had influenza It lasted four or five months, became reduced with the improvement in the Basedow's disease and finally disappeared entirely, the other signs could be distinguished for years afterward Scholz (320) observed a paresis of the right *abducens* and a complete paralysis of the left in the case of a 27 year old woman H MacKenzie (918) observed a mild paresis of both *recti laterales*

A leftsided *oculomotorius* paralysis, in Jendrassik's case (see above), included a series of signs of paralysis

Gauthier (1104) told of a 38 year old female with good heredity in whose case the disease began with continuous occipital headaches, a slight paresis of the four extremities and bladder weakness Two months later Gauthier found, besides the signs of Basedow's disease, a paralysis of all the exterior branches of the left oculomotor After temporary improvement the paralysis of the lower extremities increased, the respiration became wheezing in character, the speech was disturbed, and the patient died suddenly There was no autopsy

In a case of Dehove (699) about which Ballet (747) reports in detail, there was a bilateral *ophthalmoplegia exterior* without ptosis. The patient was a 32 year old man who showed the signs of Basedow's disease and an extreme hysteria.

A few days after a plunge into the sea, a man who had previously been healthy, but who came from a family with tainted heredity, showed unusual irritability. After a few weeks came cardiac palpitation, swelling of the neck, protrusion of the eyes, and a loss of energy. A year later Debove recognized signs of Basedow's disease, disturbances of the sensation, loss of position sense, and a globus hystericus. Six months later Ballet found a left complete hemianaesthesia, a right hypesthesia, falling toward the

dischromatropsy, monocular diplopia, loss of hearing, and loss of taste and smell occurred on the left There was a bilateral facial weakness The voice was nasal, the patient choked easily. If he swallowed fluids they came out of the nose The signs of Basedow's disease were clearly displayed.

An interesting case of associated visual paralysis, which affected only lateral gaze, was observed by v. Stellwag (235). It was a woman in her twenties

The lines of vision were usually parallel to one another and to the median line The convergence faculty was not disturbed in any way If an object was brought near, in the median line, the eyes followed, with a definite narrowing of the pupils, up to a distance of 6 5 cm They were able to retain this degree of convergence for quite a while But if the convergence object was brought much closer, or moved from the median line to one side or the other, the fixation ceased at once The head remained unmoved. Raising or lowering movements were entirely undisturbed, but only from the primary position or from symmetrical convergence Lateral gaze was impossible. Diplopia was absent About three weeks after a series of choking attacks and enlargement of the thyroid gland, there was a troublesome diplopia as both eyes seemed turned inward. Movement of the fixation object right or left was followed to middle position, but one eye remained in the adduced position, nearly unmoved. The innervation of the associated lateral movement had established itself, but complete *abducens* paralysis had come about with simultaneous secondary contraction of the medial rectus muscles. Four weeks later the *abducens* paralysis had become reduced Unfortunately nothing is said about the condition of the *nervi faciales*

A convergence paralysis with undisturbed associated movements for all directions of gaze is certainly a rare occurrence in Basedow's disease. There are few cases of convergence paralysis in this illness mentioned in the pertinent literature. From the description, they do not, however, represent exactly the disease pattern of a convergence paralysis, but rather a high

Mannheim (1222) noted, among 47 cases from Mendel's polyclinic, a 30 year old man with a weakness of the right *rectus medialis* and *superior* and of the left *rectus medialis* and *lateralis*.

In one case of G. v. Voss (2352), a 22 year old female, complicated eye-muscle paralysis occurred simultaneously with an exacerbation of Basedow's disease. There was a paralysis of the right *rectus superior* and a slight paresis of the *abducens*, on the left there was a paralysis of the *rectus inferior* and of the *abducens*. Furthermore, there was a slight facial paresis on the right. During the observations over a period of two months great variations took place in the degree of paralysis. Sometimes the disorders were more evident in the *abducens*, sometimes in the *oculomotorius*. Occasionally the movements of the eyes were almost normal. The variations were evident, sometimes, even from one day to the next.

Campbell Posey (2423) saw a woman of 43 with pronounced Basedow's disease, a paralysis of the left *abducens*, the left *oblique inferior*, and of the *rectus superior* and *inferior*. Four years later the same author (2692) described two more cases of eye-muscle paralysis symptoms in Basedow's disease. A 42 year old woman had an isolated paralysis of the right *rectus superior* and the *inferior obliques*. In the case of a 45 year old woman with severe Basedow's disease, Maude (1057) found a moderate ptosis on both sides and few days later a left-sided paresis of the upper facial branches. Two days after that limited ophthalmoplegia began to develop on the left. The paralysis of single muscles was not total. After 2 weeks, with improvement in the general malady, the paralysis diminished. Four cases of Jones (1048) included a 31 year old female with signs of Basedow's disease and a right *facialis* and *abducens* paralysis which was probably to be traced to a brain tumor manifested by bilateral papillitis, total blindness, headaches, vomiting, and sensitive areas on the skull.

In the case of a 15 year old girl about whom Marina (1469, p. 217) reports, there seems to have been beside the Basedow's disease, a slight paresis of the *recti superiores*, a paralysis of *both abducens with convergence position of the eyes, and no* diplopia. The disorder was probably congenital. In another case reported by Marina (ibid. p. 328) a 41 year old man with Basedow's disease had an *abducens* paralysis associated with a high grade arteriosclerosis of the cranial arteries.

A slight ptosis of both lids was found by S. West (686, case 31) in the case of a 31 year old woman. Whether this had any connection with the Basedow's disease can not be determined. Mannheim (1222) noted a slight ptosis twice among 47 cases. A moderate ptosis of the left upper lid with pronounced retraction of the right was observed by Vossius (1387) in the case of a 22 year old woman, and Wilbrand and Saenger (2033) noted the same in the case of a 39 year old woman. In both cases the symptom complex of Basedow's disease was incompletely developed. In the first case improvement in the malady was followed by disappearance in the difference in the width of the lid apertures, in the second case the ptosis increased in spite of improvement *in the general condition. In a case reported by Morse (2865), a 38 year* old woman, there appeared on the right a slight exophthalmia, slight retraction of the upper lid and a well developed von Graefe's sign, while the left upper eyelid appeared distinctly drooping. The pupil was equally large on both sides and reacted well. A case of Basedow's disease reported by Bartholow (1937) was accompanied by a ptosis and neuritis of the lower extremities during the climacteric.

§128. In reviewing the ophthalmoplegia occurring in Basedow's disease we have frequently encountered a paralysis of the bulbar nerves (the cases of Warner-Bristow, Jendrassik, Chevalier, Ballet, Maude, Rothmann, G. v.

Finlayson (892) observed in the case of a 32 year old patient with Basedow's disease, a rightsided *oculomotorius* paralysis occurring especially in the right temple; this went away again very slowly. A 23 year old female patient of S. West (686) suffered paralysis of the left *rectus medialis* A patient of Passler (892) had a paralysis of both medial eye muscles In one case of de Giovanni (830) there were predominantly rightsided signs of Basedow's disease and a paralysis of the right *oculomotorius* involving the *rectus superior* A 45 year old patient of Schlesinger (1073) had suffered from Basedow's disease for three years For 18 months he had an isolated paralysis of the right *rectus superior* In one case each Chvostek (269, II observ.) and von Roth (341), observed that movement of the eyes upward was entirely, or almost entirely, inhibited A 38 year old woman about whom Ditisheim (1293) tells had, besides parasthesia of the legs and paresis of the shoulder muscles, a temporary lameness of the right *rectus medialis*, and the right pupil, together with a rightsided ptosis L Bruns (2268), found in the case of a middle aged patient with Basedow's disease, a leftsided ptosis and bilateral paralysis of the *rectus medialis* and *rectus superior*. (There also was a chronic nephritis) An isolated trochlearis paralysis of the left eye was observed by Terson (2242) in the case of a 33 year old woman with leftsided eye signs and a moderate tachycardia In the case of a Basedow's disease patient a paresis of the *musculi recti superiores* was recognized On the right the paralysis was almost complete, on the left it increased during the course of the disease (Ohlemann 2866 and written report)

A grouping of the paralyses in the region of several eye-muscle nerves is sometimes combined with paralysis of other nerves, as in the following cases. Schoch (50) and Kochen (53) tell of one case, under the observation of M H Romberg, with paresis of both *recti laterales* and a lameness of the right *rectus medialis* More complicated were the conditions in the case of Féréol (303) Eight months after the appearance of the first symptoms of Basedow's disease the patient had severe headaches, dizziness, staggering toward the right, general tremor, and diplopia Diplopia occurred when the eyes were in a certain position A reduction in muscular strength on the right was discovered together with a slight muscular atrophy of the extremities on the right, a diminished sensitivity to temperature, an increase in the reflexes bilaterally, but mainly on the right, a hyperalgesia on the right, and reduction of pain sensitivity on the left The examination of the eyes showed a right-sided paresis of the sphincter pupillae and of the accommodation, and a diplopia in the right upper portion of the field of vision An exact determination of the paralyzed muscles is not possible from this insufficient description Only this much is sure it could not, as the author assumed, have been a trochlearis paresis In the subsequent course (Féréol 335) an *abducens* paralysis appeared in place of this eye-muscle paresis Ballet (533 and 803) declared that a part of the manifestations observed in this patient were hysterical

O Kahler (775) mentioned a young male with typical Basedow's disease and paralysis of various eye muscles on both sides.

Rothmann (1146) tells of a 23 year old man, previously a heavy drinker but apparently never syphilitic who was suddenly seized by cardiac palpitation and soon afterward by other symptoms of Basedow's disease There was, at that time, an insufficiency of convergence but no eye-muscle paralysis Half a year later a moderate ptosis was found on both sides The lateral and medial movements of the eyes were limited. The right eye lagged when the gaze turned upward. Pupils and accommodation were normal Crossed double-images increased their difference in height with upward gaze. There was an increase in lateral gaze toward right and left and a normal reaction to electrical stimulation.

Such a case with ptosis and pronounced involvement of the exterior eye muscles has been observed by Remak (1905). A 30 year old lady first came under medical care because of transitory double vision and afterward because of protrusion of the eyes. The malady was diagnosed as Basedow's disease and, with fluctuations, developed more and more distinctly the typical symptom complex; only the goiter and the v. Graefe's sign were absent. Together with this a slight ptosis and an *ophthalmoplegia exterior* with conspicuous changes in the paralytic manifestations on different days

ing out the tongue, puckering the mouth as if to whistle, and swallowing, could not be executed after a few repetitions. The same symptoms appeared in the extremities. This diagnosis was confirmed by Jolly. A short time later death occurred. No autopsy was made.

A case similar in many respects was reported by Meyerstein (2412). A 33 year old seamstress without hereditary taint developed a double diplopia, *this, however, did not trouble her very much. Three months later weakness in the neck muscles de*veloped and soon afterward the patient found it necessary, after a pause for rest, to give up her work because of weakness in the arms and the characteristic symptom of tendency to rapid fatigue. The eyelids often drooped. At about this time cardiac

weakness of all exterior eye muscles, a moderate protrusion of both bulbi, infrequency of blinking, a fist-sized goiter said to have been present for 20 years, a slight tremor of the hands, a pulse rate of 110 to 130 per minute, and increased perspiration. The lid closure took place without force. The longer the eyes remained open the more the ptosis increased. Myasthenic signs were conspicuous in the muscles of the upper extremities and there was distinct myasthenic reaction in both biceps muscles, as well as in the left deltoid and *supinator longus*. Three weeks after the first examination a sudden episode of dyspnea occurred. Speech and swallowing became difficult. A few days later the lips became cyanotic, the respiration superficial and rapid, the pulse very rapid, respiration ceased, and the heart stopped two minutes later. Unfortunately, permission to perform an autopsy was denied.

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held closed for a few minutes, could be almost completely raised again at the first attempt. But it soon began to sink again. After sleeping the patient could open the eye more easily. The right *levator palpebrae superioris* was easily fatigued and lid closure on both sides was feeble. Myasthenic reaction was demonstrable in the *mus. deltoideus* and *supinator longus*. Furthermore, the patient was excitable and extremely emaciated. A protrusion of both eyes was found, that on the right more distinct than that on the left. Pulse rate was 140 per minute, with a non-pulsating goiter, a tremor of the hands, and a pronounced insufficiency of convergence.

Another patient, a 35 year old female, had been suffering from Basedow's disease for several years when the upper lids began to droop. Later ptosis became complete. The lid closure was weaker than normal and its weakness increased after fatigue. Chewing and swallowing were difficult. Long conversation tired the patient. In the neck muscles, arms, and legs fatigue came quickly. A distinct myasthenic reaction was demonstrable in the left *sternocleidomastoideus* and in the *deltoideus*.

Voss). A case of this disease with paralysis of the bulbar nerves has also been reported by Bourget (810) from the clinic of Grasset in Montpelier.

Several times an isolated facial paralysis has been observed in Basedow's disease, as by Potain (498), Vigouroux (740), Cohen (1031) in a 40 year old female, Baylac (paralysis of the upper branches on both sides in a 40 year old female reported by Faure (1305), and by Passler (1362, the lips and gum branches)

Acute Bulbar Palsy

§129. In some rare cases, acute bulbar paralysis with fatal outcome is associated with Basedow's disease.

In a case of Basedow's disease with very acute course, a 13 year old girl described by Dana, crossed paralysis with bulbar signs set in shortly before death. The autopsy showed a lesion of the medulla and the bordering region of the pons G Rankin (1241 and 1493) reported a woman who for years had had a goiter without experiencing any discomfort up to the beginning of the climacteric years Then an acute development of Basedow's disease occurred Soon afterward the signs of bulbar paralysis were added leading to a fatal outcome The patient was neuropathic by heredity and had over-exerted herself mentally before outbreak of the acute manifestations L Bruns (2268) saw in a case of Basedow's disease the signs of bulbar paralysis several weeks before death These included disturbances in swallowing and chewing, and, later, in flow of saliva There was also a dysarthric disorder of speech, paraphasia, and, finally, total insanity In the case of a 50 year old woman with severe Basedow's disease described by Kelin (2393) rapid loss of strength and elevation of the previously normal temperature set in 3 days before death. Speech became nasal, indistinct, and finally incomprehensible as the result of a drop of the lower jaw The act of swallowing became difficult and finally impossible A marked sense of fatigue developed in the extremities Tachycardia, dyspnea, and coma preceded death The changes in the medulla and bulbar centers will be discussed under the Pathological Anatomy of Basedow's disease

Myasthenic Palsy

§130. We now have to concern ourselves with the combination of Basedow's disease and *myasthenia pseudoparalytica* or myasthenic paralysis This malady, the nature of which is not yet sufficiently understood usually includes a bilateral ptosis and paralysis of the exterior eye muscles A profound fatigue of the muscles and conspicuous fluctuations in the degree of weakness and paralysis are involved here. Demonstrable anatomical features in the nervous system are neither constant nor characteristic.

This combination, since greater attention has been paid to it, does not appear to be so extremely rare as one was inclined to assume a few years ago. Up to now, to be sure, few carefully observed cases are at hand.

belonging to the syndrome of Basedow's disease stood out more or less clearly. These included a slight exophthalmia in cases where this could also be attributed to an existing ophthalmoplegia, a slight goiter, tachycardia and sometimes, in isolated cases, a rapid tremor and the von Graefe's sign (see §55 above)

Very recently Fr. Chvostek (2899), in an ingenious exposition, has tried to show that a disorder in the functioning of the parathyroid lies at the bottom of the myasthenia He calls attention to the fact that the signs of myasthenic paralysis and of tetany are, in their essential features, diametrically opposed to each other But both have features in common which probably indicate a single factor. An absence or an insufficiency of the parathyroids leads to tetany. Greatly increased or qualitatively altered function of these vascular glands produces the signs of myasthenia. With the close anatomical relationship between the thyroid gland and the *glandulae parathyroidae* it is certainly not surprising when both glands undergo a disorder of function occurring in the same direction

E. Meyer (2950) emphasized that frequently a persisting thymus and general *status lymphaticus* with a relative lymphocytosis was found in the cases of myasthenia mentioned in pertinent literature as also in his own case In Basedow's disease a general muscle weakness (see §125 above), a relative lymphocytosis (see §227 below) and a persisting thymus are found together.

Hemiplegia

§131. Hemiplegia without signs of an apoplectic attack has been encountered in patients with Basedow's disease several times With the exception of two cases which ended fatally, this usually improved after a short time or it disappeared entirely

Chvostek (332, 42nd observation) found in the case of a 48 year old man with pronounced Basedow's disease a right-sided hemiparesis and a paralysis-like weakness of the neck muscles A 30 year old female patient of Clarke (818), after a two-year attack of Basedow's disease with great irritability and chorea, developed a leftsided hemiplegia, soon followed by outbursts of rage and hallucinations In the case of a 32 year old woman with Basedow's disease and chorea (see above) observed by Bradshaw (051), a right-sided hemiparesis suddenly appeared after a two year course of the disease, There was no paralysis in the face and sensitivity was retained The paralysis of the lower extremities soon improved to such an extent that the woman could stand again, but the right hand remained weak for a long time In a case of Béclère (1814) a transitory hemiplegia followed by a *monoplegia brachialis* occurred after a Basedow's disease which had been unsuccessfully treated by surgery. A 59 year old woman patient of the Marburg Psychiatric Clinic (Gause 2175) developed, shortly before the death, a leftsided paralysis of the mandibular nerve This quickly disappeared again In the brain, a small ecchymosis on the floor of the

From the French literature comes one case which belongs here, unfortunately very incompletely reported Briss and Bauer (2470) demonstrated this patient to the Neurological Society in Paris A 46 year old female had a typical case of Basedow's disease As a consequence of vomiting which could not be controlled, she had become emaciated, showed diffuse muscle atrophy, and displayed various bulbar and spinal signs which the observer regarded as myasthenic.

A 27 year old man, observed by G E Rennie (2955), fell ill with symptoms which aroused suspicion of tabes Soon afterward exophthalmia, tachycardia, goiter, and increasing weakness appeared There also was a tendency to quick fatigue of the chewing muscles and the extremities, as well as of the deep reflexes Myasthenic reactions were demonstrable There existed, in addition, an intermittent glycosuria.

It is probable that in one or another of the cases of *ophthalmoplegia exterior* in Basedow's disease (§127) myasthenic paralysis must be considered This, it seems to me pretty certain, holds true for the case of Suckling as far as one can judge from the very meager description Oppenheim (2107, p 111 and 134) and Goldflain (2183, p 301) believed they could proclaim the case of Jendrassik (see above, p. 183) also as *myasthenia pseudoparalytica* It seems to me, however, that this claim was made incorrectly, first, because the especially emphasized behavior of the eye during a change of position of the head has as yet not been observed in any case of myasthenia, second, because of evidence of a distinct atrophy of the *pectoralis dexter* muscle, and third, because of the continued reduction in reaction to electric current in the region of *Nn faciales* A case of Oppenheim cited by Warner-Bristow (see above) was complicated by disturbances in sensation contractures and epileptiform seizures Liebrecht (p 184) reported a case in which ptosis as well as bulbar signs seem to have been absent That these and Rothmann's case may be diagnosed as myasthenic paralysis seems to me very doubtful at least

Nevertheless, when an ophthalmoplegia with bilateral ptosis develops in the course of Basedow's disease one must observe carefully whether it does not owe its origin to the occurrence of a *myasthenia pseudoparalytica* Attention will be directed, above all, to the very characteristic variability in the degree of the ptosis, to a possible weakness of the lid-closing muscles, to an abnormal tendency to fatigue in chewing and swallowing, to a nasal tone in the speech, to an abnormal tendency to fatigue of the head and neck muscles and other muscle groups In the absence of any trophic disorder in the musculature and tests of a myasthenic reaction all this should not be overlooked

We may probably assume that the combination of Basedow's disease with myasthenic paralysis is not a purely accidental combination of the two diseases but that a closer relationship exists and that Basedow's disease, perhaps, prepares the ground upon which the myasthenia tends to develop more easily. Also, it is conceivable that both symptom complexes are produced by the same toxic damage. Isolated cases are known in which an illness which brought with it a toxic action existed at the same time as the myasthenia or preceded its occurrence. Also, a large number of cases are found in the literature of myasthenic paralysis in which the symptoms of myasthenia predominated in the picture of the disease. Single signs

contracture of the lower extremities Ballet believed he could attribute to hysteria the hemiparesis and hemianasthesia with transitory aphasia which developed in a case of Panas (496), a 40 year old female with Basedow's disease Also, in a case of Basedow's disease of Murchison, quoted by H MacKenzie (918), hemiplegia was pronounced hysterical. The same doubless holds good for a paresis of one upper extremity arising without evident cause and without loss of consciousness in the case of a 31 year old woman described by Boeteau (1022) The patient had suffered from general nervous disorders for a long time and, since the occurrence of the Basedow's disease, from mental changes In a case of Basedow's disease reported by Cheadle (223) of a 15 year old girl, the slight paresis of the right arm with a simultaneous contracture is to be considered hysterical, as is an almost complete paralysis which Dreschfeld (2485) observed He maintained it to be entirely functional

Complications Involving Spinal Disorders

§132. Angiolella (1087) found, in the case of a 49 year old patient with Basedow's disease, paraplegia associated with increased tendon reflexes but no anesthesia. The autopsy showed a dorsal myelitis and in other parts of the spinal cord "slight indications of inflammation". The *medulla oblongata* appeared normal.

A 45 year old woman experienced a thoroughly stormy course of Basedow's disease, observed by C Reymond (1143) Shortly before death, paraplegia with anasthesia, nasal voice and mental disturbances appeared. Except for hyperemia of the brain no macroscopically observable changes in the nervous system could be found

§133. In the case of a 50 year old female reported by Drummond (702) manifestations of an atrophic spinal paralysis (*poliomyelitis anterior*) were added to the signs of Basedow's disease. Cardiac palpitations and a general weakness had been present for years. Vomiting and general weakness confined the patient to bed. At this time, a swelling of the thyroid was discovered which soon was followed by a paralysis of the legs Meanwhile, the symptom complex of Basedow's disease became more and more complete. The paralyzed lower extremities seemed greatly emaciated Death occurred during an exacerbation of the paralysis and its extension to the diaphragm. The autopsy showed distinct anatomical changes in the anterior horn of the spinal cord in the lumbar region

A case of Basedow's disease combined with amyotrophic lateral sclerosis was observed by Ulrich (2028)

A 45 year old woman, who had been healthy up to her thirthith year showed the full pattern of Basedow's disease at forty one Two years later her gait gradually became unsteady The patient often collapsed suddenly while walking In the following spring, during reduction in size of the goiter, and the occurrence of edema in the legs, paresis of the arms, hands and legs gradually developed, the speech became stammer-

fourth ventricle was found, but no other change. Dinkler's 42 year old patient (1711 and 1954) developed after a 2 week's relapse of Basedow's disease spontaneous jerking movements of the right arms and of both legs This was followed by a sensation of prickling and "falling asleep" in the left hand and a paralysis-like weakness of the

These sometimes

eaking and eating

developed and, in

In the meantime, a conspicuous alteration of personality became noticeable. Death followed an interval of increasing mental disturbance

On a few occasions the appearance of hemiplegia has coincided with the first development of the signs of Basedow's disease or has preceded them a little

Thus Tessier (146 and 366) saw a temporary hemiplegia during the development of Basedow's disease Ballet (535, obs VI) observed a 49 year old female who had displayed hysterical manifestations in her youth and who had suffered from cardiac palpitation for a long time Seven years previously, while taking a walk, she had a sudden attack of dizziness without loss of consciousness This episode was followed by a marked weakness in the upper and lower extremities of the left side At the same time, cardiac palpitation became more intense and more signs of Basedow's disease gradually developed although exophthalmia remained absent during the entire period of observation

Cohen (1031) reports a 29 year old female who, for 4 years, had suffered from palpitations and frequent dizzy spells with loss of consciousness After such an attack two years previously a rightsided hemiplegia occurred with a speech disorder associated with weakness of the tongue and difficulty in swallowing After about four weeks the hemiplegia improved but palpitation increased and there developed a swelling of the thyroid gland and bilateral exophthalmia Paresis of the right leg and reduction in the sensitivity of the right half of the body was still present at the time of the examination there Another case of Cohen, a 32 year old female, had severe heart palpitations 16 years previously, and tremor of the hands 6 years previously She had frequent epileptic attacks for 4 years (see above, §121) A leftsided hemiplegia followed a violent seizure After that the symptom complex of Basedow's disease became complete At the time of presentation no motor paralysis could be determined any longer but there was anasthesia and analgesia of the upper extremity.

J Russell Reynolds (932) mentioned that among his 49 Basedow cases he had twice observed a slight paresis of the left arm In both cases a difficulty with articulation in speaking was observed at the same time.

If signs of hysteria are present in addition to symptoms of Basedow's disease the question arises as to whether the paralytic manifestations are not caused by hysteria.

Thus Cardarelli (514) observed a woman who developed the chief signs of Basedow's disease a few days after a bad fright hystereo-epileptic attacks and a transitory leftsided hemiplegia There was also a general tremor and a permanent

contracture of the lower extremities. Ballet believed he could attribute to hysteria the hemiparesis and hemianasthesia with transitory aphasia which developed in a case of Panas (496), a 40 year old female with Basedow's disease. Also, in a case of Basedow's disease of Murchison, quoted by H. MacKenzie (918), hemiplegia was pronounced hysterical. The same doubless holds good for a paresis of one upper extremity arising without evident cause and without loss of consciousness in the case of a 31 year old woman described by Boeteau (1022). The patient had suffered from general nervous disorders for a long time and, since the occurrence of the Basedow's disease, from mental changes. In a case of Basedow's disease reported by Cheadle (223) of a 15 year old girl, the slight paresis of the right arm with a simultaneous contracture is to be considered hysterical, as is an almost complete paralysis which Dreschfeld (2485) observed. He maintained it to be entirely functional

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any work. Tonic and clonic cramps occurred in the left arm There was a flexion spasm of the fingers and elbows A year and a half later the patient became aware that the left arm was shorter and the left hand smaller than the right Only then did the goiter, which had been present a long time, begin to swell Cardiac palpitations occurred upon slight exertion and a year later the symptom complex of Basedow's disease was fully developed. The left arm could not be raised above a horizontal position. The upper and lower arms were somewhat flexed, the deltoideus region was somewhat flattened, and the small muscles of the hand had completely disappeared There was a paralysis of the *extensor carpi ulnaris*, the *adductor* and *opponens pollicis*, and the *mm interossei* of the left side Also, the sensitivity in the extremities was weaker on the left than on the right and temperature sense was entirely lost on the left side Reaction to electric current was entirely lost in the atrophied muscles Huber (772) had observed a quite similar case In the case of a 19 year old girl there was, in addition to the original condition of cramps in the left hand and the left arm, an atrophy of the entire left upper extremity There was a marked atrophy of the *deltoideus*, the forearm musculature, of the thenar muscles the hypothenar muscles and the interossei In this otherwise well nourished patient the thinness and short length of the left upper arm was conspicuous Later a paralysis-like condition developed in this extremity This was followed by weakness of the legs and a leftsided hemianesthesia Only now did the signs of Basedow's disease develop fully By electrical tests of the atrophied muscles a reaction of degeneration was demonstrated, but fibrillary tremor was absent

In a case of L du Cazal (616) a 53 year old female developed, simultaneously with tremor and the other signs of Basedow's disease a general atrophy of the muscles of the face, of the trunk, and of the extremities

A 20 year old female patient at the Cracow Medical Clinic, whom Miesowicz (2413) reports, noticed, about four months before the first signs of illness that the upper extremities became easily tired during work and that they had become noticeably thinner General weakness, pain in the stomach region, vomiting and a tremor of the whole body followed Upon admission two months later a severe case of Basedow's disease was recognized A great difference in the development of the upper extremities was striking at first glance The more careful examination showed that the *pectoralis major* and *minor*, and still more the *deltoideus* and *trapezius*, and most of all the *supra* and *infra spinatus*, the *serratus anticus major*, the biceps and triceps were so atrophied that one could feel only a few muscle bundles through the skin The forearm and hand muscles were less affected by atrophy Yet the spaces between the bones of the hand seemed distinctly sunken The passive movements of the upper extremities were well preserved, the active ones slow and weak Strength as measured by the dynamometer was considerably reduced In the lower extremities only the muscles of the gluteal region showed a moderate atrophy Fibrillar twitching was not observed in the muscles Taste, temperature and pain sensitivity were unaltered

A year later Miesowicz (2546) again observed a case of Basedow's disease with muscular atrophy The patient was a 24 year old woman who had become afflicted by general nervousness, weakness, diarrhoea, and attacks of perspiration two years before. These symptoms were followed by the development of a goiter, tremor of the hands, cardiac palpitation and an increase in the general lassitude The complete symptom complex of Basedow's disease appeared, in addition to atrophy of the muscles of the upper extremities, especially the *m pectoralis*, *deltoideus*, *cucullaris*, *supra-* and *infraspinatus*, and triceps The muscles of the forearm and of the biceps

ing, and the patient choked easily A pronounced atrophy of the lower arm muscles, the *interossei* and the *thenar* and *hypothenar* eminences could be shown No mention is made of the spastic symptoms so characteristic for this disease Statements of its further course are lacking We learn only that therapy did not affect the process

Progressive Muscular Atrophy

§134. Some cases of paresis with circumscribed muscular atrophy develop in the course of Basedow's disease or even with its first appearance It is difficult to determine whether these are of spinal or neural origin, or due to circumscribed damage to the anterior horn of the spinal cord or to a neuritis of the motor nerves, or in fact are caused by a primary muscular disease In a number of the cases it can scarcely be doubted that it was a form of progressive muscular atrophy Most frequently the muscles of the shoulder girdle, and the biceps and brachialis and the small muscles of the hand are affected The sensitivity to electrical stimulation is reduced in the muscles involved In severe cases a degeneration reaction is also demonstrated Contractures are absent as a rule. The sensitivity remains undisturbed, in exceptional cases it was found reduced.

Dreyfuss-Brisac (615) observed a case in which, besides the main signs of Basedow's disease paresis of the right arm with an uninterrupted tremor and atrophy of the right forearm, the thumb, the finger muscles and the *m. interossei* occurred. The sensitivity was reduced in the area of *n ulnaris* Also, in a case of Silva, (638) Basedow's disease was combined with muscle atrophy in the forearm, especially the *m interossei* Cardarelli (514) saw in the case of a patient with Basedow's disease with other conspicuous nervous symptoms also a *hypertrophia* of the hand muscles; and in the case of a 12 year old girl with the same disease he noted a *pseudohypertrophia musculorum*

Bathurst (1268) found in the case of a 20 year old man with no hereditary taint the full symptom complex of Basedow's disease associated with a moderate atrophy of the *deltoidei*, and an almost complete atrophy of the biceps of both arms The muscle seemed like a fibrous cord, shortened so much that the forearm could not be extended. The triceps on both sides seemed not involved The extension of the wrist could be only incompletely performed but flexion was well carried out. The ternary muscle was atrophied The facial muscles and those of the trunk seemed to be intact A slight atrophy of the muscles of the thighs and the calves was perceptible but the muscles contracted well The feet had a tiptoe posture Toes were drawn upward The patient walked on the balls of the toes and the heels were 7½ cm above the floor

Ditisheim (1293), among 17 Basedow's cases from the Eichhorst Clinic described 2 with partial muscle atrophy. In the case of a 17 year old girl atrophy of the *m. pectoralis major* was present on both sides, there was a flattening of the deltoideus but pronounced tremor of both arms. In the second case, pain and twitching of the left hand was noticed by a 19 year old girl two years before the appearance of the first signs of Basedow's disease, the symptoms being such that she could not perform

following day he had a feeling of weakness in the limbs, a day later the limbs gave way, and, with a sense of increasing fatigue, the patient collapsed. A total paralysis of the right leg was discovered, with a loss of the right knee jerk and a weakness of this reflex in the left Soon afterward, the right leg could again be moved a little and the knee reflex was demonstrable But the patient was unable to stand up or remain upright after being placed in this position. The arms could be brought to a horizontal position only with great difficulty There were pains in the muscles of the upper arms and the *plexus brachiales* were sensitive to pressure On the evening of the same day the patient was unable to move either arms and legs or trunk and head. Urine had to be removed by catheter During the night a heavy perspiration occurred, especially in the lower extremities The next morning the patient regained complete use of all of his limbs Two more slight relapses of short duration occurred in the following weeks Signs of hysteria were absent But the symptoms of Basedow's disease continued to develop and the patient assumed a cachexic appearance

A milder case of this sort was observed by G v Voss (2352) in a 34 year old woman There was a weakness of the flexors of the upper and lower legs and of the extensors of the feet, especially those on the left Adduction and abduction of the leg was weak on the left Tendon reflexes in this case were definitely increased There was definitely no hysteria.

In a very acute, fatal case reported by Th Diller (2169) severe symptoms of Basedow's disease were associated with manifestations of multiple neuritis with rapidly increasing muscular atrophy Ten weeks after the beginning of the disease this 46 year old female had pains throughout the body These increased from day to day Every slight movement of a limb increased the discomfort Simultaneously, there developed a muscular atrophy with increasing loss of strength in the extremities and the trunk

In the case of a 50 year old man with Basedow's disease for about 3 years, there occurred, as Perregaux (1233) reported, severe pains in the right shoulder, following a fall on some stairs Soon afterward the arm could no longer be raised and lateral rotation of the arm became difficult The right shoulder appeared less fully rounded; the biceps and brachialis were distinctly atrophic The muscles involved showed a degenerative reaction The author stated, and it seems to me correctly, that the unusually rapid appearance of the paralysis, with muscle atrophy, after the fall on the right shoulder and a rather minor pull on the roots of *n circumflexus humeri*, as well as of *n subscapularis* and *radialis*, is to be attributed to the influence of the already existing Basedow's disease

A case reported by Bartholow (1936) developed during the climacteric It included ptosis and a neuritis of the lower extremities Gangrene in the right foot also developed

It cannot be definitely decided whether or not a case of Boinet and Bourdillon (950) belongs to this category, beside neuralgic pains in the *trigeminus* and in the *plexus cervicalis*, a paresis of the right arm and of both legs was present

Tendon Reflexes

§136. The tendon reflexes usually show no essential change in Basedow's disease When such change is discovered it is found to be intensified corresponding to a general increase in irritability. It is usually reduced or not demonstrable in Basedow's disease Paraparesis has been mentioned

showed no atrophy On the other hand, the hypothenars, especially the left showed signs of atrophy The active movements were weakened A degeneration reaction was not evident, but only a slight reduction in the reaction to electric current Fibrillary twitching was absent Later on the skin of the lower legs became thick (see §214 below)

A Money (674) saw *in the case of a 29 year old female with typical Basedow's* disease atrophy of the masseters Voluntary actions as well as the reaction to electric current remained intact Vigoroux (740) found, besides paraplegia, an atrophy of the *sternocleidomastoideus* without any change in sensitivity to the electric current Oppenheim (2214 and 2417, p 1037) found an almost complete atrophy of the gluteal muscles in the case of a patient with Basedow's disease

In the case of the 30 year old female of Kahler mentioned above (§124), with a possibly hysterical paraplegia and contracture of the legs, the greatly emaciated extensor muscles of upper and lower legs were nearly powerless, but not paralyzed. Only the extensor muscles of the feet and toes and the *peronei* seemed completely paralyzed as well as greatly emaciated The electrical excitability of the muscle complex of the lower leg could not be determined because of a scleroderma (see §217 below) existing at the same time, the thigh showed a somewhat reduced sensitivity In the case of a patient with Basedow's disease and hysterical symptoms of Charcot there was, besides the paraplegia, an extreme emaciation of the legs (see §124 above)

Liebers (2852) reports a case combining a childhood dystrophy of the facial muscles, signs of Basedow's disease, tachycardia, goiter, exophthalmia, and tremor This combination probably must be considered accidental

In the cases with progressive atrophy, the anatomical changes in the muscles described by Askanazy (1690) with which we shall later become more closely acquainted (see Pathological Anatomy of Basedow's *disease*) may not be discussed at this point, as Miesowics attempts to do. For the changes found by that investigator are, in the first place, of a different nature, and, in the second place, represent not a combination of Basedow's disease with progressive atrophy, but a general emaciation which, as we shall see, is a very frequent sign in severe forms of that disease.

Multiple Neuritis

§135. In a few cases, the signs of paralysis can possibly be traced to a toxic multiple neuritis probably dependent upon the Basedow's disease.

Ditisheim (1293) tells of a case from Eichhorst's Clinic, a 38 year old woman Besides the symptoms of Basedow's disease she suffered from parasthesia in the legs, a sense of coldness of the feet, loss of the knee reflexes, loss of strength in the upper and lower extremities, paresis of the left *nervous peroneus* and of the shoulder muscles, especially the left deltoid. There was also a transitory paralysis of several eye muscles (see §127 above)

Rosenfeld (2227) described from the Strassburg Psychiatric Clinic the case history of a 19 year old man who had suffered for two years from moderately severe Basedow's disease Two days after a cold foot bath he had headache and nausea On the

cannot well be attributed to the progressive muscle atrophy accompanying Basedow's disease.

A 24 year old female with a leftsided hemianesthesia was reported by Mannheim (1222, p. 133). The signs of hysteria were distinct Similarly in the case of a woman of 32 (p 135) all sensation over the right side was distinctly impaired The right hand distinguished only between hot and cold objects The senses of touch and taste were reduced on the right side of the tongue Perregaux' case (1233) of a male of 19 is of comparable interest Together with a right hemianaesthesia he had many indications of hysteria (see below 145)

A female of 40 treated by Stiller (793) had a severe case of Basedow's disease which became inactive during a trip to the Riviera The cardiac embarrassment seemed to improve. Then she had a sudden right hemianaesthesia This was associated with neuralgia and other paresthesias, but no loss of consciousness and not the slightest disturbance in motor functions The neurological findings indicated a hemorrhage or embolus involving the posterior limb of the internal capsule The usual question arises as to whether this was a hysterical sensory loss Stiller reports that this woman with a familial history of nervous disorders, and in a setting of agitation and grief, developed a clear cut episode of Basedow's disease "on a hysterical and neurasthenic basis" In one of the cases among Oppenheim's observations (855) hemianaesthesia and hemiataxia was associated with Basedow's disease for a short time The histological section showed a thrombosis involving the proximal wing of the internal capsule (see below 143) This case was a female of 42 Among Benedikt's group (348 p 670) a boy of 19 recovered sensation over the right side of the head after 2 months Although tactile sense had been present, it was subnormal In the subsequent course of this illness the characteristic signs of Basedow's disease became apparent

Cohen (1031) reported a case from the Mendel Polyclinic, a female of 36 with poor heredity had epilepsy since her 19th year, and for three years had symptoms of Basedow's disease (see above §118). She complained of painful pulling sensations in the left leg and a sense of numbness in the hands. A hypalgesia in the entire right half of the body was discovered together with a motor weakness of the right arm and both legs.

Two other cases of Mendel were described by Mannheim (1222, p 130) A 26 year old and a 40 year old woman. In each case the sensibility of the right half of the body and of the extremities was reduced In the first there was also a motor weakness of the right leg and a prickling sensation in the right foot In the second case signs of hysteria were absent, but signs of an accompanying tabes were present (see §144)

Various paresthesias may be associated with Basedow's disease.

A diffuse unilateral paresthesia occurred in the case of a 19 year old male patient of

[illegible]

left arm of a 21 year old woman whose sister suffered from a pronounced hysteria (p. 129)

Other patients complain that the legs frequently go to sleep, the feet feel numb, and that there is a prickling and tickling sensation in the hands and feet

above (§124) It sometimes happens that the tendon reflexes seem increased for a time and later return to normal Even if they are absent it is *usually only temporary.*

Kocher (2197), among his numerous cases, has never found a variation in the condition of the tendon reflexes Passler (1362) noted, in 6 of his 51 cases, "very active" tendon reflexes Also, H Volkmann (799) reports 6 Basedow cases of which 4 had intensified knee jerks Among 16 cases in which Mannheim (1222) made a notation about the condition of the patellar reflexes, they were normal in 9 and increased in 1 case, a 36 year old man with very conspicuous nervous symptoms and in another of a 32 year old woman with definite signs of hysteria In 2 cases they were diminished and in 4 cases absent In 3 of these cases there were also a number of signs of tabes (see §144 below) and in 1 of these, buckling of the legs was troublesome Hopfgartner (905) reported the absence of tendon reflexes in the case of a 19 year old female patient with Basedow's disease J Wiener reported from Mendel's Polyclinic an advanced case of this disease involving a female, age 22, whose examination showed a total absence of the patellar reflexes The author is inclined to attribute this absence to tabes

The various reflexes sometimes show quite different behavior Bodensteiner (2045) reports a 45 year old female from the Ziemssen clinic. The patellar reflexes were somewhat diminished at first Later, with an advance of the disease and the nervous symptoms, they seemed noticeably increased. The diaphragmatic and conjunctival reflexes were lost but the gag reflex was present In a second, severe case of a 24 year old female, the lower reflexes, the knee jerks especially, were lost, the upper body reflexes, however, were increased The gag reflex was absent

Sensory System

§137. Sensory disorders do not really belong to the symptom pattern of Basedow's disease Nevertheless, various kinds of disorders of sensation have been observed in a number of cases These are partially conditioned by a multiple neuritis with paresthesia like that in a case of Ditisheim (see §135 above) In a great majority of the cases the paresthesias may be attributed with more or less certainty to an hysteria complicating the Basedow's disease. In a few cases, finally, the relation of paresthesia to Basedow's disease cannot be determined with certainty.

The right-sided hemianesthesia with color blindness and loss of taste and smell on the right side, which was discovered in Warner's (533) 25 year old female patient, in the later stage of the disease, by Bristow (640) may, I believe, be definitely designated as hysterical (see §127) In the cases of Debove (699, see §127) and Panas (496, see §131), Ballet correctly regarded the hemianesthesia accompanying the paralysis as hysterical The same interpretation would apply also to a leftsided hemianesthesia observed in Huber's case (772, see §134), and in the case of a 19 year old patient mentioned by Ditisheim (1293, see above) At any rate, these disorders in sensitivity

Headache and Hemicrania

§138. *Many patients with Basedow's disease complain of headaches.* Frequently they described it as a general, dull pain; in many cases the headache is rather localized in the back of the head, the top of the head, the forehead, or sometimes, on one side. Fluctuations in intensity and frequency occur often Not infrequently they are more severe in the morning

Passler (1362) mentioned headaches among his 51 cases 32 times (63 74%) They were very distressing and formed the chief complaint of the patients Kocher (2197) found them in 82 5% of his numerous cases, in 3 cases on one side only They were rarely continuous, and frequently more severe in the morning In many cases they occurred among the first signs of the disease Among Murray's (2213) 120 cases headache is noted only 6 times. (Perhaps they were only noted when a spontaneous complaint was made) Among my 95 cases they are recorded 24 times, once on one side only.

§139. In isolated cases the headaches have the character of a typical hemicrania

Among 51 polyclinic patients of Passler (1362) this was the case 5 times In the case of a 32 year old woman the previous migraine disappeared after the symptoms of Basedow's disease had developed A 50 year old woman, about whom Friedmann (2373) reports briefly, had suffered for 10 years from severe headaches which occurred at intervals and lasted from three hours to five days The attacks usually came before or shortly after menstruation With the appearance of the Basedow's disease symptoms headaches had nearly disappeared But when this disease was finally cured, after a year, the headaches returned again with increased intensity Gueneau de Mussy (492) found migraine in his 4 cases, S West (686) in 2 among 38 cases, a 42 year old female had headaches two to three times a week for 7 years and had signs of Basedow's disease for two years A 24 year old woman for many years had frontal headaches in the forehead from time to time, dating from the onset of Basedow's disease she had a typical rightsided hemicrania which recurred every week and lasted 24 hours Vetlesen (1924) told of 2 patients with Basedow's disease suffering from migraine In both cases the mother or one or more brothers or sisters also suffered from it In the case of a 38 year old female, Jacobson (1739) reported that Basedow's disease was preceded by many years of a typical left-sided hemicrania which occurred at intervals of four weeks, without relationship to menstruation A conspicuous facial pallor and nausea accompanied the illness It occurred on the right side with great intensity at intervals of two weeks On the left side the signs of *sympathicus* paralysis appeared (see §68 above) Wilbrand and Saenger (2033, p 137) reported a 45 year old woman who had Basedow's disease for eight years and then complained of headache on the right side with lacrimation of the right eye (see §81 above)

In a lecture at the New York Academy of Medicine C W Cutler (1952) stated that migraine was present in the majority of cases of Basedow's

Such cases were described by Chvostek (269, observation 9), Danbresse (540), Mannheim (1222) in several cases, Kocher (2197) in the case of a 39 year old woman among others A 31 year old female patient of Saint Marie (736) often, had the feeling of both hands "having fallen asleep" for 10 or 15 minutes. The paresthesia in the legs noted by Ditisheim (1203) beside various other pareses was probably one sign of a multiple neuritis (see above §135).

Hyperesthesia seems to occur in Basedow's disease rather infrequently. Corlieu (132) reports a single case of oversensitivity of the whole body, and Roesner (340) reports the same in the hands and feet. Merklen (494) reported general hyperesthesia of the lower half of the body region in the case of a 27 year old servant girl during an acute exacerbation of Basedow's disease which she had had for several years Kocher (2197) reported hyperesthesia of the scalp in the case of a 52 year old woman with pronounced Basedow's disease and without any signs of hysteria The high-degree hyperesthesia and hyperalgesis of the feet, especially of the soles, in the case of a 45 year old woman observed by Cohen (1031), can probably be attributed to an hysteria complicating the Basedow's disease. The patient could often not endure the contact of the stockings and had frequent attacks of dizziness with hysterical crying A 41 year old male patient of Féréol (303) had an increase of sensibility on both sides. On the right there was hyperalgesia and on the left a reduction of pain sensibility. As already mentioned above (§127) a complication in the form of hysteria was probably present.

If we disregard headache, which will be discussed below (§138), we seldom hear complaints of pain in Basedow's disease. In a few rare cases the pains which do occur are to be attributed to an existing multiple neuritis (see above §135). Sometimes the pains have the character of neuralgia. They usually indicate chance complications.

A patient of v. Stellwag (235), in her 20th year, had the motility disorder of the eyes above described (see §127) and frequently attacks of an extremely violent stabbing pain which radiated from the left temple toward the top of the head, and made even any touch impossible At the same time the lower lid of the left eye often swelled to a sack-like appearance (see below §211).

Kocher (2197) reported pains in various body regions in not less than 4% of his cases He therefore does not regard them as chance manifestations. Seven of these patients had attacks of rather severe pain inside the ear and in the teeth on one or both sides These pains could be caused by compression of the *carotis communis* on the side affected even when spontaneous complaint of such pains was not made In two of these cases tetany attacks were observed (see §113 above).

hensible that this has an unfavorable influence on the physical as well as the mental state of the patient. Improvement of sleep in severe cases is to be welcomed as a favorable sign.

Sleep-walking has been observed as an unusual symptom

Among Pässler's (1362) 51 cases, sleeplessness was noted 21 times (41%) and among 20 cases of von Schulze (2118) 7 times (35%) Among Kocher's (2197) numerous patients there was disturbed sleep in 35 (43 75%) In the cases of several of these there was a more or less continuous sleeplessness In a few cases sleep had been poor from the beginning of the illness and remained entirely absent during further progress. Murray (2213) mentioned absolute sleeplessness only 4 times among his 120 observations, but disturbed sleep was mentioned as very frequent. Twenty of Riedel's 50 patients with Basedow's disease (K Schultze 2749) complained of sleeplessness Kroug (2700) considered, from his experience, that this was a frequent, characteristic, and very distressing symptom. It was noted 34 times among his 106 cases (32%). Among 59 of my own cases, in which notations about the state of sleep are given, sleeplessness is noted as either lasting or continuous 9 times (15 25%), poor or restless sleep or difficulty in falling asleep is noted 33 times (about 56%) In 17 cases good sleep was especially mentioned

In rare cases a longer or shorter period of morbid sleepiness preceded the insomnia.

Oppenheim (2107 and 2417, p 1367) observed profound sleep from which the patient could not be wakened several times Enuresis occurred also. Meige and Allard (1998) have described morbid sleepiness in the case of a 31 year old woman with *Basedow's disease*

Complications Involving Other Disturbances of the Nervous System

§142. We have repeatedly encountered cases where, concerning the combination of Basedow's disease with other diseases, the question must remain moot of whether an etiological connection between the two diseases may be assumed, a connection as to whether one prepared the ground for the occurrence of the other, or both owed their origin to one and the same cause, or whether merely a chance complication occurred. Many of these complications have been observed only very exceptionally, others are met with more frequently, and therefore arouse our interest to a greater degree. A neuropathic disposition in many cases here, also, forms the connection between the two ailments

§143. We have before us a purely accidental complication in a case published by Walzberg (371) of a tumor of the base of the skull (small-celled spindel-cell sarcoma). It is the case of a 20 year old male suffering from Basedow's disease

disease even in its incomplete forms. That is very certainly not correct Typical hemicrania, a very widespread affliction which affects especially individuals who are neuropathically inclined can indeed be considered only a complication of Basedow's disease although some degree of relationship is evident between the two diseases, as illustrated in several of the case histories reviewed above. It is different with the ordinary headache which we encounter so frequently in Basedow's disease This can be counted as a subsidiary, although inconstant symptom. General nervousness and anemia which we encounter in many of these patients may also increase the tendency to headache.

The mother of a 19 year old female patient related, as reported by Pässler (1362, p 215) that every time that the patient complained about headache her head became quite red and the eyes protruded

§140. Sometimes there is a complaint of a noise in the ears or being hard-of-hearing The former can be a vascular symptom if it occurs rhythmically with the pulse beat on both sides (see above §13)

In the case of a 54 year old female patient of Boinet (1695) the tinnitus was unusually loud and lasting The patient compared it with the sound of a steam engine. That it could not be caused by an observable thickening of the drum was shown by the fact the woman heard the ticking of a watch at 33 cm distance The sound increased at times, especially a little while after meals The attacks lasted two to three hours They were accompanied by dizziness and a feeling of coldness, although the patient otherwise complained of heat and profuse perspiration

Hardness of hearing, when it occurs in Basedow's disease is probably to be viewed as a complication.

A 47 year old woman with typical Basedow's disease, but without exophthalmia, noticed a loss of hearing after the occurrence of the disease Morrice (2325) assumed a paralysis of the auditory nerve Other paralyses were not present A 22 year old female patient with Basedow's disease reported by Eckervogt (516), had frontal headache associated with a decided reduction in the acuity of hearing in the left ear (ticking of watch at 9 cm)

Disturbances of Sleep

§141. Disturbed sleep or insomnia is a frequent complaint of patients with Basedow's disease. In many instances sleep is restless, frequently broken, and not refreshing There are lively or troubled dreams, from which such patients waken sometimes Others complain that they cannot fall asleep for a long time. In many cases there is a virtually complete lack of sleep This is one of the distressing symptoms of Basedow's disease. Trousseau has already described this in admirable fashion. It is compre-

brothers and sisters) disseminated sclerosis occurred. In one of these cases a goiter was also present but without symptoms of Basedow's disease.

Tabes Dorsalis

§144. The combination of Basedow's disease and tabes comes under observation only rarely However, there exists a series of cases in which this combination has been definitely established Diagnosis offers no difficulty when the characteristic signs of both diseases are found fully developed. But when, as it is not unusual, only single signs of the one or the other disease are developed there can be some doubt as to whether we are justified in assuming such a combination. We know, indeed, already that a temporary absence of the patellar reflexes (see §136 above), a paraparesis even suggesting an ataxia, and parasthesiae of many kinds (§137) can occur exceptionally in Basedow's disease On the other hand it is known that, as Charcot has already shown, chronic tachycardia is not very rare in tabes patients, and can sometimes be discovered early Even attacks of anxiety, suggesting angina pectoris, with tachycardia and cardiac arhythmia can arise Spasmodic coughing attacks with negative laryngoscopic findings occur, exceptionally, in each of the two diseases (see §182 below) Joffroy (837 and 838) thinks, incorrectly in my opinion, that tabes, by itself, can also produce a slight protrusion of the eyes, especially in older patients.

Among 7 tabes patients with Basedow's disease signs demonstrated by Joffroy, only 3 cases could be considered as showing coincidence of the two diseases In the cases of the 4 others the rapid pulse was probably a tabes symptom, and the slight protrusion of the eyes mentioned in 3 might well have been a habitual state

In the case of a 29 year old woman who had suffered from attacks of hysteria for 16 years, there was, aside from a well-defined tabes, a slight protrusion of the eyes and a pulse rate of 80 beats per minute A 42 year old woman had suffered for two and one-half years from complete atrophy of the optic nerve Also, the right eye protruded somewhat Her pulse rate was 106 A 60 year old woman whose tabetic signs had been noted since her forty-fourth year, had previously, between her twenty-fifth and thirty-fifth year, suffered from cardiac palpitations and had always had protruding eyes These had also been characteristic of her mother At the time of examination a slight cardiac hypertrophy and pronounced tachycardia were evident together with the signs of tabes (110 to 130) Other signs of Basedow's disease were absent In the case of a 39 year old patient who had suffered from tabes for 12 years, a rapid pulse (80 to 100) occurred, and also a barely perceptible goiter which had been present for a long time

The occurrence of the two diseases in relation to time may vary. There are quite a few cases when this cannot be definitely determined from the statements of the patient. The examination merely shows the characteristic signs of the two diseases concurrently, more or less complete

An accidental combination was presented in the hemianesthesia and hemiataxia caused by a hemorrhagic accident of the posterior portion of the internal capsule in the case of a 42 year old woman who had suffered from Basedow's disease for about half a year before death, as described by Oppenheim (855). Stiller's case (§137) would also belong here: in the course of a severe Basedow's disease a temporary rightsided hemianesthesia developed, if we wish to accept the interpretation of the observer.

The discovery, reported by Joffroy and Achard (1119), of a syringomyelia (*gliosis spinalis*) together with an angioma in the posterior cranial fossa in the case of a 37 year woman suffering from epilepsy, choreiform twitching of the left arm, contracture of various muscles, and Basedow's disease (see above, §118), indicates a purely accidental complication. The same complication existed in a case of Spillman (2580).

P J. Mobius (558) described the combination of *paralysis agitans* with Basedow's disease in the case of a 50 year old woman. Later (1478, p 54) he again returned to the case and thought he had probably erred, in the previous diagnosis. It seems to me, however, according to the description given in 1883 of the pattern of the disease that, although exophthalmia was absent, the other signs—tachycardia, palpitations, goiter, nervous restlessness, sleeplessness, great sweating, and emaciation—are distinctive for Basedow's disease On the other hand, with the exception of increased perspiration, they can be brought into the symptom complex of Parkinson's disease only with constraint. The characteristic Basedow's disease tremor was replaced by the form of trembling peculiar to shaking palsy. I would therefore, have no hesitation in holding to the original interpretation.

A Gordon (2378) also has had an opportunity to observe this rare complication Besides signs of Basedow's disease a woman patient of 39 exhibited the posture of trunk and hands, the permanent muscle tension, the statue-like staring expression of the face, and the peculiar continual trembling characteristic of paralysis agitans

It is also a matter of a complication in cases in which progressive paralysis is added to a Basedow's disease which has already been present for some time.

Savage (568) tells of a 39 year old man Goiter was absent from among the signs of Basedow's disease Two additional cases are described by Boeteau (1022) One was a 27 year old woman, with poor heredity, observed by Berbez In this patient both diseases, fully developed, progressed together, the second was a 38 year old male drunkard under Targlowa's observation, in this case an inherited tendency and a luetic infection were acting together.

E S Reynolds (2425) observed a case in which multiple sclerosis and Basedow's disease occurred in combination Soon afterward he saw a girl with pronounced Basedow's disease among whose relatives (in 3 among 6

a slight weakness of the lower facial muscles, and diminished sensation over the *distribution of the right radial nerve. There were also many signs of* Basedow's disease and eruptions of an urticarial rash (see below 194) Kollarit's series (1746) includes a female of 42 who had signs of tabes for 7 years For 6 years she had headaches, vomiting spells, nervous instability, and a disturbing tinnitus A year afterward she developed a goitre, exophthalmia, tremor, and some minor signs of Basedow's disease which persisted up to the time of her death a month later The case demonstrated before the Budapest Medical Society by Hudovernig (2516) was similar A 53 year old female had an unsteady gait, shooting pains, and impaired vision for 6 years In the final year she had multiple paresthesias, enlargement of the neck, headaches, marked sensitivity to heat, and drenching sweats The examination revealed a high grade exophthalmia, infrequent blinking, a tremor, cardiac dilatation, tachycardia, a right lateral rectus weakness, and additional signs of tabes There was a history of a miscarriage and a child lost at 12 months

There are also cases in which the tabetic signs were added to an already established case of Basedow's disease.

Charcot (816–817) describes such a case A 42 year old man whom Mobius observed had suffered a syphilis infection 15 years before For several years he had cardiac palpitations and an enlarged thyroid To this was later added shooting pains between the lower jaw and the larynx These became unbearable after much walking The removal of a large part of the thyroid gland did not lessen the pain Möbius observed a definite carotid pulsation, tachycardia, a fine tremor of the hands and a minimal exophthalmia The eyes were described as somewhat staring There was a loss of pupillary light reflexes Shooting or stabbing pains were present in the legs as were bladder disturbances The pains in the throat gradually disappeared Delearde (1838) observed a 26 year old female who had acquired syphilis 15 years before, and one year later an enlargement of the thyroid gland Cardiac palpitations and protruding eyes were noted Ten years later signs of tabes appeared At the time of the examination the signs of both diseases were present

From the polyclinic of Mendel, different writers have published several cases which showed the presence of a smaller or larger number of tabetic signs in addition to Basedow's disease Wiener (1018) reports a woman who had the complete pattern of Basedow's disease, together with a loss of patellar reflexes, and a furry sensation in the soles of the feet In three cases which Cohen (1034) describes the signs of both diseases were very clearly displayed A 32 year old nervously afflicted woman had one abortion and had lost three children for reasons attributed to cerebral softening with spasms She had cardiac palpitations for sixteen years, a tremor for six years and epilepsy for four years (see §121, below) Then the Basedow's disease symptom complex became complete. In addition there were stabbing pains in the legs, bladder disturbances, and other signs of tabes

A 42 year old woman with fully developed Basedow's disease of 5 years duration experienced progressive loss of patellar reflexes, a staggering gait when eyes were closed, a slow light response of very small pupils, shooting pains in the legs, a sense of constriction, incontinence of urine, and ataxia of the hands and legs.

A 45 year old female had a goiter for fifteen years and, for eight years, a cardiac palpitation, heavy perspiration, sensations of heat, and diarrhea For four years before, she suffered from stabbing pains in the legs, a sense of numbness in the feet, a sense of constriction, an unsteady gait, and double vision A number of other Basedow's disease and tabetic signs were also displayed

There was the case of a 49 year old female patient of Joffroy (837–838). The symptoms of tabes had gradually developed over a period of ten years and were said to have been the consequence of a violent emotional disturbance at the time of menstruation Furthermore, there was an exophthalmia, a rapid pulse (84 to 90) and an occasional slight tremor of the hands Distinct goiter and carotid pulsations were absent The combination of both diseases was mentioned again by Joffroy (1117)—without further information concerning the time sequence—and in a later report of the two diseases in a female hysteria case; by Barié (804) in a man; by Secchieri (861) in 3 cases, by P Marie and Marinesco (1130) in the case of a woman of 36, and by Achard (1807) in the case of another woman

In several cases the signs of the two diseases seem to have appeared simultaneously.

In the case of a 56 year old woman observed by Joffroy (837–838) signs of tabes had been present for four to five years For about the same length of time, she showed an accelerated pulse, exophthalmia and an occasional slight trembling of the hands Ingelrans (1591) reported a 62 year old female with a hereditary trait The patient had been highly nervous since childhood Ten years previously, upon cessation of menstruation, the symptom complex of Basedow's disease and of tabes had developed gradually In the case of a 53 year old male patient studied by Mobius (1480), there was a previous history of syphilis One after the other, pains in the limbs, double vision, weak vision, trembling, pounding of the heart, and general weakness occurred In addition, there was a loss of pupil reflexes, an atrophy of the optic nerves, an oculomotor spasm on the right side, an absence of knee reflexes, a staggering gait (when the eyes were closed), and beside all these the chief signs of Basedow's disease

In one series of cases the tabes had lasted at least twice as long before the Basedow's disease began.

Joffroy's patient of age 48 (837 and 838) had been tabetic since he was 35 He then developed all the major signs of Basedow's disease There had been a goitre since he was six years old Brissaud (1277) observed from the beginning of the illness a patient whose progressive paralysis preceded tabes and Basedow's disease Two of the cases at Mendel's polyclinic showed signs of tabes A female of 41 reported by Lewinneck (1606) had lightening pains and paresthesias for 3 years. Then a small goitre present since age 13 began to grow and at the same time there were palpitations, drenching sweats, and a tremor The physical findings included fixed pupils, eye muscle palsies, amblyopia, ataxia, and a disturbance of bladder function All the characteristic signs of Basedow's disease except the eye signs were present A woman of 51 whose history is contributed by Timotheeff (1159) and Mannheim (1222) contracted syphilis at the age of 24 From the somewhat unreliable history it appears that for between 5 and 7 years the signs of tabes had included shooting pains in the legs, sacral area, and abdomen, impaired visual acuity, and epigastric pains Signs of Basedow's disease had been present for a year At the time of the examination she had fixed pupils, early optic atrophy, contracted visual fields, eye muscle palsies, loss of the consensual light reflex, absent knee jerks, a positive Romberg, an ataxic gait, a disturbance of bladder function, gastric crises, lightning pains, tremors, numbness of the feet, an appreciable shift of the extruded tongue toward the right,

the floor of the fourth ventricle in Basedow's disease and upon certain experimental evidence with which we shall become acquainted later. Ballet correctly emphasized [illegible]

also because Barié's views have been offered in support of the bulbar theory of Basedow's disease.

Much more weight should be given to the fact that in a number of cases a previous syphilitic infection was definitely established or seemed probable from the case history Unfortunately, in many of the accounts of the disease, as reported, insufficient attention has been given to this causal factor which is so important to the development of tabes. We shall see later that syphilis also plays a part in the etiology of Basedow's disease (see below under *Etiology of Basedow's Disease*), *although its significance is not yet* fully explained.

Hysteria

§145. Hysteria is by far the most frequent of all nervous ailments which in association complicate Basedow's disease In the previous paragraphs we have repeatedly had occasion to point out this complication Signs of hysteria, or the entire symptom complex of this disorder become evident in fact rather often with Basedow's disease Charcot (816) declared that the combined occurrence of the two diseases is very frequent Among twenty four cases, mostly from the salt-peter works, which Renault (934) reported, hysteria was diagnosed in three patients, one of them a girl of twenty, another twenty four, and in a nineteen year old male The latter had frequent attacks of hysteria and localized painful spots in the *iliac fossae* Among 16 Basedow's disease cases collected by Dienot (1709) there were two with signs of hysteria, one of these was an 18 year old girl and one a woman of 32 In the last case the signs of astasia abasia had been present for four years Among the 47 cases assembled by Mannheim (1222) 10 had signs which could be attributed to a complication with hysteria Pronounced hysteria occurred in 5 cases among the girls and women between 21 and 32 years of age. *Hill* Griffith (608) noted only 1 case of pronounced hysteria among his 32 Basedow cases J. Russell Reynolds (932), on the other hand, estimated that he had met with instances of hysterial attacks in 25% of his 49 cases (48 of these were women).

The frequency of occurrence of this complication seems to vary considerably in the various countries and centers of observation on the prevalence of hysteria By far the larger number of observations originate in France, and especially in the Paris hospitals.

In the case of a 40 year old woman whose case history was described by Mannheim (1222, p 130), there were cardiac palpitations and an enlargement of the thyroid gland for twelve years following childbirth. The goiter increased steadily together with exophthalmia, tremor, and a series of other signs of Basedow's disease Later various signs of tabes appeared a delayed pupillary light reflex involving particularly the small right pupil, paraesthesia and reduced sensitivity in the extremities, loss of the patellar reflex, a feeling of constriction, shooting pains, and stomach cramps

A 45 year old woman had pronounced Basedow's disease without the eye signs for several years During its course uncoordinated and slow light reflexes, a staggering gait when the eyes were closed, a feeling of numbness in the soles of the feet, and a sense of constriction were added The patellar reflex was retained

A 49 year old female, reported by Timotheff (1159), was afflicted, after fright and excitement, with cardiac palpitations which gradually increased and which were the only symptoms noticeable for two years These were followed by a sense of pulsation in the throat, diarrhea, a feeling of numbness in the soles of the feet, stabbing pains in the legs, and general weakness Added to the symptom complex of a Basedow's disease in which exophthalmia was absent, there developed a fixation of the pupillary reflex, the Romberg sign and a retention of the skin reflexes with loss of all tendon reflexes

A patient who had a goiter for a long time and showed the signs of a mild but distinctly developed Basedow's disease, visited M Burnhardt (2615) The complaint was not caused by the above symptoms but by difficulty in walking and in bladder function Aside from the slightly atactic gait, an absence of the patellar reflex, a pronounced Romberg sign, a circumscribed hypaesthesia, and a reduction of sensitivity to pain were recognized A syphilitic infection was denied and the Basedow's disease as well as the other ailments of some duration were attributed to overwork. It was noteworthy that the wife of this patient was likewise very active in the business, often had to lift heavy weights, and that she suffered from typical but mild Basedow's disease

From the review given above it must be concluded that, in the majority of carefully described cases, the separate signs in the two diseases do not occur at widely divergent intervals One gets the impression that any mutual damage increases a tendency to the appearance of processes which were going on jointly anyway In many cases a more or less pronounced inherited or acquired neuropathic disposition leads to this tendency. Ballet (803), Joffroy (838), E Boix (2362) and others have emphasized this especially. On the other hand, the expressed opinion of von Barié (8041) that the Basedow's disease symptom complex in the course of tabes is no chance coincidence, but rather the sign of an extension of the processes to a further degree, analagous to other already known bulbar disturbances, would definitely contradict this view.

Barié assumed that certain other changes would occur following an originally congested condition of the medulla oblongata, especially a degeneration of the *tractus intermediolateralis*, as described by Pierret These changes were the cause of the vasomotor symptoms He bases this upon the finding of a small hemorrhage of

Oesterreicher (600) reported a family in which the mother suffered from hysteria and eight of ten children were afflicted with more or less fully developed Basedow's disease. Five of the daughters also had distinct hysterical symptoms. In an instance reported by Laschenk (987) the mother of a patient with Basedow's disease was afflicted with the same sickness and also hysteria. I wish to add here that the 18 year daughter of the 50 year old woman mentioned above, with leftsided hysteria signs and rightsided Basedow's disease signs, reported by Féré (1962) showed just these same hysterical manifestations of the left half of the body, without, up to that time, displaying signs of Basedow's disease.

Among the patients with the complications of Basedow's disease which we are considering, the proportion of females is conspicuously predominant, just as for the noncomplicated hysteria with which we are at present acquainted. A remarkably high proportion of the patients is youthful. The youngest was 12 years old. In the case of a 45 year old woman, a 52 year old woman and a 59 year old woman the hysterical attacks had been occurring for years and, indeed, in the 52 year old patient dated from her early youth.

In the majority of cases the definite pattern of hysteria was either present before the appearance of Basedow's disease or the case history demonstrated that the patient had been suffering from hysterical attacks for a long time. Occasionally we learn that the mother or some brother or sister once had suffered from hysteria or still does. In other cases signs were discovered in the course of the Basedow's disease which were to be attributed to a complicated hysteria. It also happens that, during the development of this illness an existing hysteria diminishes and reappears to a pronounced degree from the point on where the Basedow's disease approaches a cure. Such a case was observed by Charcot (816) in the history of an 18 year old girl. In the case of another patient the signs of hysteria developed progressively as the signs of Basedow's disease improved by electrical treatment. Hudovernig (2516) reported a woman in whose case, during the high point of the Basedow's disease, hysteria diminished, only to reappear later in the form of climacteric hysteria following the cure of the disease.

In several cases it has been demonstrated that hysteria did not appear until the Basedow's disease was in progress. I draw attention to the two cases of Appelt (2143) mentioned above. In one of these hysteria occurred simultaneously with an exacerbation of the Basedow's disease.

Although darkness reigns in regard to the actual nature of hysteria we are indebted to a series of outstanding studies for symptomatology of disease so exact that there is not much room for doubt in the demonstrated cases in which the diagnosis of this complication figures. It is otherwise, however, with the interpretation of isolated nervous and psychopathic symptoms which occur in the course of a Basedow's disease. In regard to paraplegia, which doubtless must be viewed as a genuine symptom of this

I recall the cases already referred to above, those of Féréol (303) in a 41 year old man (§127), of Panas (496) in a 40 year old woman (§131), of Debove (699) and Ballet (747) in a 33 year old man (§127), of Charcot (816, §124) and of Boeteau (1022, §131) Ball (278) and Raynaud (338) described a 24 year old woman who had suffered from Basedow's disease for two and a half years and also displayed conspicuous signs of hysteria P Marie (555) told of a 45 year old female with an incompletely developed Basedow's disease and hysterical signs which already existed before the appearance of the first signs of this illness Aubry (80) mentioned this combination in the case of a man, Renault (931), in the cases of a man and two girls (see above), Joffroy (908) in the case of a 25 year old woman, R. Martin (921) in that of an 18 year old girl studied by Charcot, Brunet (1092) in the case of a 25 year old girl, Dienot (1709) in the case of an 18 year old girl and of a 32 year old woman (see above) There are also cases of Grasset (972), Boinet (1695), Raviard (1778), Debove (1836) In the case of a 37 year old woman studied by Joffroy and Achard (1118) repeated attacks of hysteria were interspersed in the course of Basedow's disease A 52 year old woman had been hysterical from her youth, and had Basedow's disease from her 36th year, with varying severity Chr Féré (1692) observed a 59 year old woman who for many years had hysterical attacks involving the left side He found a left hemianesthesia including smell, taste, hearing and sight associated with a hemiparesis To these were later added rightsided signs of Basedow's disease including protrusion of the right eye, v Graefe's sign on the right, a tremor of the fingers of the right hand, and a pulse rate of 120 per minute The hysterical manifestations improved in later years and partly disappeared, the Basedow's disease signs remained unaltered and of moderate intensity

Perregaux (1233) has acquainted us with such a case from Switzerland The very pronounced Basedow's disease of a 19 year old male was complicated by severe hysteria, a right hemianasthesia, a concentric narrowing of the field of vision of the right eye, and attacks of hysterical spasms occurring chiefly at night During these he threw himself about, struck out, howled like an animal, and then wept By pressure on the abdomen the attacks were unmistakably influenced for the better From Italy comes a case of Cardarelli (54), that of a woman who had a severe fright (see above, §131) Cheadle (223), Hill Griffith (658), Maude (1057), Kelley (410) and Ch.S.Potts (2223) each report one such case among many observations J. Russell Reynolds (932) as already mentioned, observed a larger number O Becker (453) stated that several of the Basedow's disease cases which he investigated, displayed a high degree of hysteria In Mendel's polyclinic a number of such cases have been observed Of these a few have been reported bv Cohen (1031), the majority by von Mannheim (1222) (see above) Thingen (2587) reported a case of Basedow's disease involving a 25 year old woman worker and complicated by severe hysteria J. A Hirsch (2675) studied a case of a 15 year old girl who was not neuropathically tainted Besides the typical signs of Basedow's disease hysterical muscle spasms were present The patient had hysterical attacks during which a paralysis of the extremities and speech occurred which lasted about half an hour Bornikoel (2267) reported a soldier with incompletely developed Basedow's disease and hysterical epileptiform attacks associated with a prolonged rise of body temperature

In 2 cases of Appett (2143) severe hysteria developed during Basedow's disease following an accident Steiner (1513) observed a 12 year old girl who had suffered from cardiac palpitation since her sixth year In addition to the typical signs of the disease, excitability, episodes of anger, forgetfulness, numb areas over the back, and hyperaesthesia in the loins were experienced.

and that the hypersecretion of the thyroid gland can in itself be a sign of hysteria, such assertions must be emphatically denied.

Neurasthenia and Traumatic Neuroses

§146. It is not surprising that neurasthenia also appears in company with Basedow's disease since the latter prefers to attack individuals with a neuropathic predisposition. It affects chiefly male patients Headache, sleeplessness, a fine rapid tremor, cardiac palpitation, tachycardias, vasomotor disturbances of various sorts, paraesthesias, a tendency to fatigue, a feeling of weakness, great exhaustion with every kind of mental activity, depressed moods and increased excitability are manifestations occurring in both diseases When such a complication exists it is difficult or indeed impossible to determine whether one or another of the symptoms mentioned is attributable to this disease or to the other But we far from agree with Boeteau (1022) when he surmises that neuraesthenia frequently accompanies Basedow's disease and when he attributes several other disease symptoms to this *accompanying neuraesthenia*

Erb (2002) admits that he believed for a long time that Basedow's disease represents a form of neuraesthenia characterized by a special localization of functional disorders and symptoms He has partly renounced this opinion

Berbez (806) has described a distinctive case of this combination in a male and J. Faure (1305) that of a 30 year old female A 39 year old laborer observed by Flatau (1963), has already been mentioned (§47) This case is a fine example of this sort. Flatau decided upon the diagnosis of neurasthenia

§147. It also does happen that Basedow's disease develops together with symptoms of a traumatic neurosis or an accident hysteria

A case of this sort has been published by B Witmer (2034) from the Kronlein clinic A 48 year old man was struck on the head by a 35 kilogram oil cask from a height of at least one meter It cannot be ascertained whether he lost consciousness A week after the accident, nausea and an epileptic attack occurred The latter was repeated two or three times within twentyfour hours A week later a violent *tremor* and occasional cardiac palpitation occurred Later, there was a moderately severe exophthalmia He complained of severe pains in the throat and in the back of the neck and became extremely excitable Nine weeks after the accident the excision of a part of the goiter, which he had for a long time, seems to have relieved the suffering only slightly

An interesting case, belonging here is contributed by Tetzner (2772) In February, 1900, the left arm of a 19 year old laborer became entangled in a transmission and the man was hurled about He was thrown so that his head struck the ceiling, from which he fell four meters This accident resulted in a dislocation of the right arm and severe concussion of brain and spinal cord Four weeks later he took up light

illness, doubt must sometimes arise. We have already discussed the differential diagnosis (§124) and also have mentioned cases in which hysteria plays a part In many cases of hemiplegia and paralysis of single parts of the body we have pointed out the possible connection with a complicated hysteria and we have shown pertinent examples (§131) Usually the paralysis is in the nature of an hysterical paralysis Sometimes a contracture is combined with it (see above, §124 and §131). It may be that certain of the spasmodic conditions described *as epileptic attacks in Basedow's disease* had the significance of hysteria (see above, §122). A vibrating rapid form of tremor can occur in hysteria also as mentioned before; we have indicated the difference between this and the typical Basedow's disease tremor (§96) Choreiform movements, when they are observed in Basedow's disease, can be part of a complicated hysteria. Then they have a more rhythmic character Sometimes choreogenous zones are discoverable. We have mentioned such a case above (§116) We have already thoroughly explained and illustrated, by a series of cases, that it is not always easy to determine to what extent certain psychic disturbances in patients with Basedow's disease are to be attributed to an accompanying hysteria. Various disturbances in sensitivity, hemianaesthesia, hypalegesia, parasthesia of many sorts, hyperasthesia, and hyperalgetic zones in the case of such patients must always suggest a complication with hysteria. Other signs of hysteria are also likely to be discovered Sudden and unpredictable changes in the manifestations are also characteristic of hysterical insanity to a high degree

Such observations were reported by Ballet (747 and 875) in the case already described of a 33 year old male, by Joffroy (908 a and b), in that of a 25 year old woman and that of a 35 year old woman, by Brunet (1092), in that of a 25 year old girl; by Mannheim (1222) in that of a 21 year old female and a 32 year old female, and by Stammen (2347) in that of a 55 year old female

Lack of appetite alternating with voraciousness, anorexia, vomiting, diarrhea, outbreaks of perspiration, pytalism, polyuria, and various vasomotor disturbances are disease manifestations which may belong to one or the other of these diseases. The complete pattern with a rapid change of symptoms and perhaps also a susceptibility to influence by suggestion may be used to determine the relationship to hysteria.

Many authors certainly go too far when they not only point out certain nervous manifestations and other secondary symptoms common to both diseases that make the differential diagnosis difficult under some circumstances, but also raise doubt that these indications are to be interpreted as hysterical At a time when the symptomatology of Basedow's disease as well as that of hysteria still was only slightly known and not clearly circumscribed, it is not remarkable that Bruck (16) described the manifestations of Basedow's disease in his nervous patients as hysterical, misinterpreting the nature of the protruding eyes Moreover, this observer later (112, 1862) admitted that he had erred in regard to the hysteria. But when in our time

opinions are expressed to the effect that, probably in the majority of manifestations of Basedow's disease nothing but hysteria of a special form is indicated and that one may speak of a hysteria caused by thyroid gland poisoning (A Pader 1895), and that the hypersecretion of the thyroid gland can in itself be a sign of hysteria, such assertions must be emphatically denied

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work After eight months he was sent to an institution for observation because he complained of pain in head and neck and weakness in the right arm Except for a slight increase in the skin and tendon reflexes nothing abnormal could be discovered A pension of 35% was agreed upon Later this was reduced, and, on July 1st 1905, entirely withdrawn Half a year later the man again reported ill. A psychoneurosis with severe depression and cardiac neurosis was diagnosed by the doctor. Two months later the entire symptom complex of Basedow's disease was noted. There were a number of other symptoms characteristic of hysteria

§148. A quite unusual and certainly extremely rare complication of Basedow's disease was the affliction called pseudo-Menière vertigo by Frankel-Hochwart, presented by these observers (2659) to the Society for Internal Medicine and Pediatrics in Vienna.

A female patient, 26 years old, five years previously had often lost consciousness but had no spasms For several months she had displayed signs of Basedow's disease. Furthermore, she often suffered from headache, tinnitus, and dizziness. Many attacks ended in vomiting The dizziness displayed was of the Menière type, in which the patient did not actually become dizzy and did not have to lie down but saw everything going around in circles about her The auditory system was entirely normal

Changes in Mental State

§149. An alteration of mental state is a constant sign of Basedow's disease Cases occur very rarely in which, during the whole course of the disease, such a change is not observed by those surrounding the patient and by the doctor, and such cases are usually of the less severe kind Most frequently unusual sensitiveness, excitability, and restlessness is manifest which those around the patient simply call nervousness, and which seems especially strange in those persons who were previously known to be calm and selfcontrolled. In many patients personality and character change entirely They seem to be transformed People who previously were of gentle disposition and considerate, and those who had a high degree of self control, grow angry at the slightest occasion, become quarrelsome, inconsiderate, demanding, argumentative or even untruthful. They appear ungrateful, discontented with everything and make life around them very difficult People who were formerly energetic often lose their energy, and although they become increasingly active they are incapable of doing any methodical work, especially any continuous mental activity. Basedow (15) himself described the altered mental condition of his patients in an uncommonly significant way.

"The temperament of the patients has changed noticeably Although they were previously phlegmatic they now display a desperate cheerfulness and preoccupation, become pleasure-seeking, frequent preferably public places and promenades in spite of their strange appearance, have a certain craving for fresh air, love walking, wear

the neck, chest and arms bare, and therefore have had the misfortune to be considered crazy by the layman because, with this noticeable alteration in temperament, the speech likewise becomes unsteady and hurried"

While in many patients an unnatural cheerfulness of disposition prevails (v. Basedow 15, Geigie 181, P. J Mobius 1478, p. 33, and others) there are others—and these are, in fact in the minority—who are predominantly in a sad mood and inclined to weep They are usually fearful; the slightest outward cause frightens them and causes a high state of excitement. Many harbor thoughts of death and suicide. Sometimes the temporary anxiety states are related to attacks of cardiac palpitation (see above, §5).

As the malady continues a rather cheerful mood is often overcome by the awareness of the illness, and a state of depression replaces it But even then the excitability of the patient persists. The mental mood changes without special cause and sometimes turns into its exact opposite.

The inward unrest and disturbance of mental equilibrium betrays itself usually even in facial expression and in the whole bodily bearing. The patients display an unsteady bearing, a certain haste in their movements; they make many purposeless and involuntary movements, especially of the arms and hands. Instability is expressed also in the glance and in hurried speech. The words "tumble all over themselves" The undertaking of rather delicate investigation, as for instance, with the ophthalmoscope, is almost impossible sometimes When answering questions directed to them the patients frequently show themselves to be contradictory and forgetful Many tire the doctor with a volubility difficult to restrain They occasionally interchange words, that is, use quite other words than they intend (paraphrasia).

Bruck (112) already observed this condition to a striking degree in his 18 year old female patient It was also evident in Geigel's (181, p 73) 48 year old patient The interchange usually followed a certain sequence When he wanted to say *Hornhaut* (cornea) the word *Dornschlag* (thorn) slipped out, instead of *Medizin* (medicine) he said *Gemüse* (vegetable), etc , without noticing this himself A patient described by P J Mobius (1887) was surprised, herself, when the wrong word slipped from her tongue The disturbance occurred only occasionally There was no paragraphia Similar observations were made by Boettger (349), Cane (376), Johnstone (595), and Drummond (702, 1 case) In this latter case of Basedow's disease observed by Bruns (2268), paraphrasia was evident several weeks before the signs of a fatal bulbar paralysis appeared J Russell Reynolds (932) noted in 2 of his 49 Basedow's disease cases attacks of aphasia which occurred several times a day and lasted three or four hours

The mental disturbance of many of these patients was shown by their inability to think logically and to concentrate on one thing In many there was a noticeable flight of ideas "chorea of ideas", as it has been called not unsuitably by J. Russell Reynolds (932).

This observer has encountered it among his 49 cases several times. "The patients try to think of one thing and think of another instead. This confuses them so that they give up the effort entirely " A Maude (1056, 1346 and 1473) has seen significant cases of this sort

It is not unusual for the patients to complain spontaneously of their forgetfulness

Mannheim (1222) noted forgetfulness 17 times among his 47 cases In 1 it was of a high degree V Mieulicz (2010) noted a memory weakness in 3 of his 8 male patients Kocher's (2197) patients also complained of this

Isolated instances of temporary memory loss occur, resembling "ambulatory epilepsy", as Maude (1473) describes it.

There can occur transitions in Basedow's disease from vivid dreams (see §141 above) which the patients while awake dwell upon and follow, up to definite hallucinations and sensory illusions as well as other symptoms of a psychosis.

Among 10 of the 180 cases observed by Murray (2553) there were lively hallucinations without actual insanity A patient believed that he saw a man, who had been buried several days before, come through the door Others had more or less clear visions of men and animals before their eyes One woman thought that she heard loud quarrelling in the court and saw someone coming into the house. These hallucinations were especially vivid at night when the patients lay awake for some time

A Maude (1346 and 1473) stated that olfactory hallucinations are entirely absent in patients with Basedow's disease, while frequently occurring in cases of myxedema Yet the occurrence of olfactory and gustatory hallucinations is especially emphasized by Schenk (938) in the case of a 62 year old female, by Hirschl (2192) in that of a 24 year old male, and by Diller (2169) in the case of a 46 year old female These three cases suffered from severe forms of Basedow's disease with hallucinatory insanity (see §157 below)

§150. Not infrequently a disturbance of the nervous and psychic equilibrium is one of the first symptoms of the developing disease which causes the patient or his relatives to seek advice from a doctor The experienced practitioner will not fail to think of the possibility of a developing Basedow's disease and perhaps can already discover tachycardia and tremor

In patients who formerly were considered nervous, and in whom a lack of harmonious development of the entire mental personality has previously been apparent, sensitivity increases quite considerably with the appearance of Basedow's disease In many cases an alteration of character is apparent

Following Basedow's classic description we find the emphasis upon unusual excitability, changes in mood, a bizarre series of characteristics also given by a number of other authors on the subject such as Bruck (11, 24 and 112) Romberg and Henoch (39), Geigel (181), Aran (78), Delasiauve (299) and Trousseau (219). The latter also has pointed out that the disease frequently begins with these nervous and psychic changes. "Graves disease starts out with an extraordinary nervous irritability, with conspicuous alterations of character, etc "

§151. Several writers provide us with definite figures concerning the frequency of occurrence of increased sensitivity and pronounced alterations of mood in their Basedow's disease patients

Thus, Passler (1362) noted 38 such cases among 51 ambulatory patients (74.5%) Among 47 patients from Mendel's polyclinic about whom Mannheim (1222) reported not one was free from a certain degree of psychic disorder In most of these it consisted of excitability, restlessness and combativeness In 6 cases, cheerfulness or excitability alternated with a depressed mood In 12 the mood was predominately tearful even to a melancholy depression, in 3 of these cases this was combined with sensibility and a quarrelsome attitude In 3 cases the sad mood increased to a dissatisfaction with life and thoughts of death or suicide In 1 case compulsory hallucinations of a religious nature were combined with these In 3 cases visual hallucinations were present together with a great excitability, restlessness, and tearful moods In another case there were also auditory hallucinations Kocher (2197) never failed to find the typical forms of nervous excitability and restlessness among his numerous cases Many patients became easily excited at the slightest cause A few suffered from deep depression In others the mood changed without any apparent cause Sensory illusions also occurred A true psychosis was not observed Slight or rather severe psychic changes were recognized in 34 of the 50 patients with Basedow's disease who were surgically treated by Riedel (Schultze 2749) A Maude (1346) found psychic changes regularly but a true mental disturbance only once among 20 cases of Basedow's disease In 73 of the 120 cases reported by Murry (2213) his notations are given concerning the mental state of the patient Restlessness and suppressed excitement were found in 20 of these Hallucinations occurred in 2 patients One man suffered from melancholia with a suicidal trend In 72 of my own 92 cases, mostly observed only in the polyclinic, and in part of at least rather mild cases of Basedow's disease indications of some psychic disorder were present More or less nervous excitement and restlessness was noted in 56 patients One who sometimes was very angry stated that when she had worked off her anger her whole body trembled violently This condition disappeared entirely after thyroidectomy In 4 of these cases the mood changed frequently One woman was very susceptible to persuasion In 2 patients there was a continued mood of tearful depression A 36 year old woman suffered from hallucinations and mania which had developed gradually after an unsuccessful partial goiter excision (see §157 below) In 12 cases, among them one severe, it is especially stated that no notable disturbance of psychic behavior could be ascertained One case showed a complication with pronounced hysteria

§152. Fluctuations in the mental state usually run parallel with fluctuations in the course of Basedow's disease Nothing influences the course of the disease so much as occurrences which increase the mental excitement of the patient In occasional instances of exacerbation, the pathological activity of the mind is shown in the clearest manner Sudden unfavorable changes in the mental state accompany an acute outbreak of the disease or an acute relapse

Psychoses

§153. Almost imperceptibly, the path from the above described changes of mood and peculiarities of behavior of many Basedow's disease patients

leads to real insanity. The sudden, often unmotivated states of excitement and attacks of anger form the transition to manic episodes. In the milder forms, consciousness is not clouded, and sensory illusions or hallucinations are absent. A number of the least severe features grouped together by von Kraepelin as manic depressive insanity we also encounter in many Basedow's disease patients V. Basedow himself drew a line of demarcation between the psychic changes in his patients and those of the insane whereby he expressly insisted that the former displayed "neither a pathological imagination nor an abnormal wilfulness". A number of cases have been described as hypomanic or as "cyclic" madness in Basedow's disease. The symptoms included uncontrolled moods of cheerfulness, touchiness, anger, and hyperkinesis alternating with a depression with brooding on death. These approach the state which, in preceding paragraphs, we have described as not unusual in Basedow's disease Usually these disturbances ran parallel with the somatic changes More rarely they disappeared while the Basedow's disease continued to progress. These pecularities of psychic instability in Basedow's disease accordingly far outnumber, among the psychoses arising in this disease, those which fall into the pattern of overstimulation, intensified psychomotor stimulation, and delirium with or without episodes of depression Among 150 cases of psychosis in Basedow's disease which I could collect from the pertinent literature and from my own observations, and which I classified as far as possible, considering the frequently inadequate descriptions, over 70, that is nearly half of all the cases, belong to the group which Kraepelin has grouped together under the name of manic-depressive insanity. In this group predominantly manic conditions stand out unmistakably, from the mildest forms to the most severe attacks of frenzy. In about one third of these cases the manic episode occurred only once in a small proportion of rather mild cases, then, after it had lasted several weeks, it seemed to progress to recovery while the Basedow's disease showed no noticeable change in its course. Whether recovery from the mania was permanent remains uncertain, since reports about the further course are, for the most part, lacking In a severe case reported by Baumler (203) the death of the greatly weakened 49 year old male followed extreme exhaustion after five weeks of manic excitement and delusions of persecution. In a surprisingly large number of cases (13) death occurred in the course of a single manic attack. All these cases involved a severe form of mania and severe Basedow's disease. Usually the latter had been present for several years before the outbreak of the mania, and several times the mental state was altered to a noticeable degree even before In 2 cases the course of Basedow's disease was acute Mania appeared as a high degree of excitement, in some cases frenzy, frequently with sensory illusions, delusions of persecution and irrationality. Death usually occurred after extreme

exhaustion, or a rise in temperature with marked tachycardia, extreme excitement or acute insanity. In one instance it followed a left hemiparesis, facial paralysis (see above, §131), and deep coma The autopsy in this case showed bilateral pleuro-pneumonia and degenerative changes in the heart muscle. The brain, as in another case in which an autopsy was performed, showed a negative picture, except for a few small ecchymoses in the floor of the fourth ventricle

Arranged according to the ages of the patients, fatal attacks are reported by Drummond (702) in the case of a 28 year old woman, by Clark (818) in the case of a 30 year old woman The latter before the attack of mania suffered from a generalized chorea (see §116 above) Additional reports are those of Boedecker (808) on a 34 year old female, of Lemcke (1340) on a 36 year old female, of Drummond (702) on a 42 year old female, of Gowers (1042) on a 45 year old female, of Robertson (339) on a 47 year old male In the latter case an epileptic attack followed manic excitement which had progressed to wild raving and then had diminished After a week the patient died of violent vomiting and extreme exhaustion In the case of a 59 year old female described by Gause (2175) violent excitement occurred two weeks before death, during this time the patient was confused and had illusions of a predominantly blissful nature, a hemiparesis was followed by coma and a fatal outcome In 2 cases of Baston Jacobs (1858) the age is not reported, and in the cases of Bertoye (748) and F R B Atkinson (2254) the Basedow's disease was acute The former was a 58 year old female who, since the menopause 4 years before, suffered from nervousness, extreme excitability, loss of memory, and an indifference to external matters The symptom complex of Basedow's disease had developed only during the final weeks This included a rise in temperature, palpitations and varying manic excitement with delirium About four weeks after the onset of Basedow's disease a high state of excitement, suicidal trends and amnesia appeared followed by death in coma In Atkinson's case, that of a 55 year old man, the disease became rapidly worse and ended in death within 12 weeks One week before death manic psychosis broke out Death was preceded by hyperpyrexia, tachycardia and delirium

In a series of cases—it seems to me that about 20 reported in the pertinent literature belong here—the psychosis appeared in the form of the so-called recurring or periodic mania, meaning that, in the course of Basedow's disease, repeated attacks of mania occurred. They seldom come at regular intervals Usually they are irregular both in the intensity and length of the intervals. A distinct initial or terminal state of depression appears in isolated cases only

Among the cases which belong here, a brief initial condition of depression was mentioned 3 times by Hirschl (1208) including a 17 year old girl (1208), a 16 year old boy (2192), and an 18 year old girl A case of Johnstone (595), a 32 year old female, had alternating mania and depression Later, in the intervals between the violent manic attacks, the depressive symptoms decreased In a 20 year old girl with severe Basedow's disease described by M Mackenzie (214), the manic attacks of three or four hours duration were followed by a state of lethargy or coma Fr Peterson (733) mentioned the case of a 21 year old female who had manic episodes during which

she danced ceaselessly, sang, and acted theatrical parts, until signs of distinct fatigue became evident. This case showed also intervals of intensified self-consciousness, tendency to boldness of speech, lying, and temptation to steal fine clothes

In several cases the manic episode took on a pronounced erotic color as illustrated by a 28 year old female described by Luhrmann (1466), a 35 year old female described by Greidenberg (1108) a 35 year old female described by Bror Gadelius (1340) and by a woman who also had delusions of persecution, as in the case of a 48 year old female reported by Boinet (1695) The psychosis broke out after an exothyreopexie and improved after the operative removal of one half of the goiter

In one case it was reported that the period of manic excitement always came in the warm season of the year (Witkowski 347), a 55 year old female Basedow's disease patient who was an alcohol addict, a 43 year old woman reported by Westedt (871) had attacks of frenzy almost every evening for nine months These were apparently intensified by emotional conditions and digestive disturbances When the Basedow's disease improved markedly the psychoses were cured. In several cases the latter was spoken of as improved; in the majority, however, it remained unchanged A 38 year old female reported by Benedikt (348) developed severe mental excitement in the course of Basedow's disease. A pronounced mania appeared only in the course of the illness

Five such cases, all severe, ended fatally

A 20 year old girl reported by Morell Mackenzie (214) exhibited general restlessness and sleeplessness along with the symptoms of Basedow's disease which had been present for the previous four and a half years Repeated attacks of mania were followed by coma In the following days states of excitement of several hours duration and epileptiform attacks were followed by delirium and death C Johnston (595) observed a 32 year old patient with Basedow's disease At first excitability alternated with depression Later, a temporary violent manic excitement developed, during which she ran about, shrieked, swore, and destroyed everything she could put her hands on. After a few days of rest violent excitement returned followed by a two month interval of quiet Two fainting spells were followed by mental confusion and weakness of the left arm A month later a series of attacks occurred characterized by loss of consciousness and leftsided hemiplegia Death followed one of these attacks A softened area was found in the upper part of the anterior and posterior central *gyri* of the right hemisphere A 35 year old female reported by Bror Gadelius (1310) experienced episodes of manic excitement of varying intensity for several years She suffered from mental confusion, a fixed idea and a persecution psychosis After temporary improvement the excitement increased again with a chain of paranoid ideas Death occurred during muttering delirium A 48 year old patient of Geigel (181) exhibited increased motor impulses soon after the beginning of severe Basedow's disease accompanied by increasing sleeplessness After several periods of remission the condition grew worse, with ideas of persecution and grandeur as well as hallucinations Finally, violent manic excitement developed which lasted until death came from exhaustion. In a severe case of M. Clark (818), in a man of 46, pericarditis was the cause of death

In a large number of cases (the literature contains 27 which seem to belong here) a depressive state came to the fore, ranging from mild mental

disturbance to profoundly melancholy moods with hallucinations. In the majority of these cases psychosis was preceded by a shorter or longer interval of depression. Many patients are tortured with anxiety ideas, and suffer from guilt or persecution manias The illusions frequently have a hypochondriacal content. A 31 year old childless woman, observed by Boettger (349), had the fixed idea during strong sexual excitement that she was pregnant. Also, sometimes compulsive ideas appear, as in the case of a 40 year old woman about whom Raymond & Sérieux (1068) report Many patients have sensory illusions and sometimes definite hallucinations Others, during periods of manic excitement, exhibit ideas with a sorrowful content, and suffer from guilt fixations or persecution of which they complain loudly and incessantly There also occur mixed forms in which the symptoms of both the manic and the depressive states appear simultaneously, with mental inhibitions, sorrowful illusions, bodily unrest and an urge to activity

This condition appeared especially pronounced in the case of a 32 year old female Basedow's disease patient reported by Bror Gadelius (1310) The psychosis began with gloomy moods It was intensified through the fear that her mother would die and that the patient would become dependent upon charity Bodily unrest grew into anxiety states The patient ran out unclothed on the street, had persecution fixations, and suicidal tendencies Although quiet most of the time when she was alone, she lamented and wept loudly when anyone came near Besides motor unrest she also displayed a mental vacillation and flight of ideas as in mania After an improvement in the mental condition for almost two years, the anxiety states and the restlessness disappeared There was a return to good health but the woman became taciturn and introspective and a transition to dementia seemed to be developing

A transition to mild dementia has several times been observed in the later course of the disease.

The degree of manic excitement remains moderate in the majority of the cases belonging here, however, isolated cases have also been observed in which manic excitement increased to the point of frenzy, a destructive urge, and a tendency to soil oneself

A 23 year old female with severe Basedow's disease was observed by Leeper (1091) A mild manic state developed gradually into a semi stuporous condition which remained unaltered for over a month The temperature was subnormal during this time, and the pulse which previously was scarcely distinguishable became somewhat slower Following the administration of small doses of thymus gland extract the pulse rate increased again, the mental condition improved rapidly, and became normal The signs of Basedow's disease had also improved somewhat In a case of Keraval (described by R Martin 921), that of a 37 year old male, and in one of J Faure (1305), of a 53 year old man, at the beginning great excitement with violent outbursts of anger, followed by a depression could also be observed

A peculiar transition from stupor with attacks of mania concurrent with menstruation was accompanied by alterations in a soft slightly pulsating

goiter This case with exophthalmia, has been described by Thoma (1243) The Basedow's disease was to be sure, not typical, for during the entire course of the observations an increase in pulse rate, cardiac palpitation, a tremor and lid signs were lacking.

A 28 year old girl fell into a stupor of varying depth. The onset of each menstruation was accompanied by an increasing state of excitement simultaneous with a decrease in the circumference of the neck and a decrease or disappearance of the exophthalmia With cessation of the menstruation, which occurred irregularly, the excitement gradually gave way to a stuporous condition, the neck again swelled up and the eyes protruded once more Allan Reeve Manby (848) mentions briefly the case of a woman with typical Basedow's disease and a "semi-maniacal mental disturbance" which seemed to alternate with enlargement of the thyroid gland and protrusion of the eyes

Recovery from the psychosis has been observed in a few of the cases belonging here while the Basedow's disease remained unaltered or intensified

In the case of a 15 year old girl observed by Ganser (1436) the mental disturbance passed after several weeks A 30 year old woman described by Impacciantı (1116) developed Basedow's disease and a pronounced melancholy mood with anxiety during a pneumonia During a subsequent recurrence of pneumonia in the other lung the depression changed to violent manic excitement which terminated in complete recovery after several weeks During this time the Basedow's disease increased in severity Recovery occurred in a case of W J Collins (698) and in the above mentioned cases of Boettger and Leeper (1991)

In the great majority of cases the psychosis remained unchanged or the patients were discharged during a period of quiet and were lost to sight. In 4 cases death occurred during the stage of manic excitement

This was the case with 2 patients of Savage (568) One was a 24 year old female and the other a woman of 28 In both cases death occurred by exhaustion from diarrhea and vomiting after a short psychosis In the case of a 40 year old female described by Raymond and Sérieux (1068) death occurred during the third attack of mania A 32 year old woman described by Schultes (2230) had melancholia for several weeks, followed by an attack of excitement with a guilt fixation lasting several days This changed directly to a stuporous condition with a greatly accelerated pulse rate before death On the last day there was a left hemiplegia

If we review again the large group of psychoses in Basedow's disease which represent pure mania and manic-depressive insanity it is striking that the large majority were in the younger age group

Of 62 cases in which the age is stated 45 were between 14 and 41, and 17 of these were between 14 and 25 years of age

In the younger age group the form of psychosis which is involved seems to be more amenable to a cure.

Among 54 cases about which information concerning the further course has been given, 16 cures or cases of improvement occur among those in the younger years of life, and only 3 among those over 40.

The large number of deaths deserves attention. Particularly, since, according to general experience, a fatal outcome of the purely manic-depressive forms of insanity is infrequent, if severe injuries can be avoided. The older age group in particular is in greater danger

While 7 of the 26 Basedow patients with mania attacks between the ages of 14 and 40 died, death occurred in 9 patients among 14 over 40 years of age. Among 27 patients with a pronounced form of manic-depressive insanity, 2 of the deaths occurred in the thirties and one each in the forties and fifties

In the entire group of 22 fatal cases in which the form of psychosis under discussion occurred, death occurred with two exceptions during a manic episode (see above).

In far the greater majority of cases the manic-depressive condition arose in the course of an already present Basedow's disease accompanied by a more or less pronounced mental disturbance In a number of cases the psychosis and the Basedow's disease apparently developed simultaneously. A few times the symptom complex of Basedow's disease was discovered when the patients were presented for institutional treatment on account of their mental disturbances In only 2 cases, a 38 year old woman described by J. Faure (1305) and Impacciantı's (1116) 30 year old female patient, a melancholy mood had been present for several weeks before the occurrence of the first sign of Basedow's disease.

§154. In no small number of cases the mental disturbance with Basedow's disease appeared in the form of melancholia. This occurred not only in the case of patients in the declining years, but also in some at an earlier period of life Some of the cases in question have been designated *melancholia simplex* even by trained observers. Some were so plainly distinguishable by a complete lack of excitement states, by symptoms of anxiety, by guilt ideas, hypochondrical illusions, persecution fixations, or suicide thoughts, that, in my opinion, the psychoses must really come under the heading of melancholia Not infrequently, the patients were troubled by visions and hallucinations A few attempted suicide.

Eight patients with Basedow's disease and melancholia were between 18 and 40 Six were between 40 and 50, and 17 over 50

The psychoses were entirely or nearly cured in only 10 cases

Twice, once in the case of a 55 year old woman about whom Stammen (2347) reports, and once in that of a 65 year old female patient of Bundt (1405), the cure followed a goiter operation, and occurred simultaneously with the improvement in the Basedow's disease In the case of a 53 year old extremely emaciated woman who

was being treated by K Alt (2602) the cure was accomplished simply by suitably chosen nutritional therapy based on a careful study of the metabolism involved The patient had shown Basedow's disease signs for over three years; for the previous six months, following an episode of excitement, she had become mentally disturbed by sleeplessness, fear, stern self-reproach, and a strong suicidal trend In the course of half a year she was bodily and mentally restored and gained 23 kg in weight.

Seven cases ended in death

A 22 year old woman whose case history is given by Pilet-Fonet (1139) had a severe and acute case of Basedow's disease Autopsy showed minimal pericarditis, fatty degeneration of the heart muscle and of the liver, and hyperemia of the brain A microscopic examination of the organs showed nothing abnormal A 42 year old woman whom Dinkler (1711) observed, developed a melancholy mood with self-criticism and frightening auditory hallucinations during an acute relapse of Basedow's disease, there were also bulbar disturbances and a left hemiplegia before death (see §131 above) Hay's (975) 66 year old patient died after a series of cramps of the right side An inequality of the pupils preceded loss of consciousness In the case of another patient, a 61 year old woman whom Hay (975) observed, and in that of a 62 year old female reported by Schenk (938) death resulted from exhaustion The case of a 77 year old female patient at the Marburg psychiatric clinic was similar (Gause 2175) In addition to extreme emaciation and coronary arteriosclerosis pachymeningitis and atrophy of the brain was established Boeteau (1022) in his thesis mentions a 22 year old female patient suffering from melancholia and anxiety states who also developed a pericarditis

Among most of the cases of Basedow's disease with melancholia the psychosis followed a pre-existing Basedow's disease. In two cases the two diseases developed at about the same time in a 22 year old female and in a 47 year old female In 2 patients mentioned by Stammen (2347) the symptom complex of Basedow's disease was discovered during an examination of the mental condition; in 4 cases the pyschosis preceded the onset of Basedow's disease

A 55 year old female patient of Joffroy (908) had melancholia with illusions and hallucinations for at least 15 years before the development of Basedow's disease The latter improved very considerably while the former remained unchanged A Hay's (975) 66 year old female patient had melancholia for three months followed nine months later by Basedow's disease Another of his patients, a 61 year old woman had had a melancholic mental disturbance of three months duration for five years prior to the observation Four years later signs of Basedow's disease appeared A mild dementia preceded the fatal outcome by a year Jacquin's patient of 64 (949) had recurrent episodes of melancholia Following a 17 year remission a second attack lasted 15 months After 10 more years there was a third attack of 19 months After 12 more years came a fourth which coincided with a fall in the water 2½ years prior to the time of observation Eight months before death the final episode began in association with a Basedow's disease which progressed unfavoraby under the influence of the psychosis

§155. In a few cases the mental disturbances during Basedow's disease appeared in the pattern of a *dementia praecox*. Although some have been

described under other names, in my opinion symptoms and course described justify our ascribing them partly to the insanity of pubescence and partly to the catatonic form of insanity. Usually the duration of the psychosis extended over several years. A few times, *e g*, in a 26 year old man described by Andrews (239) and in a 30 year old man whom Bonardi (1941) observed, after initial anxiety, depression and transitory increased excitement, it developed rapidly into a deterioration of judgement, emotional instability and led soon afterward to death. Death probably resulted from the severity of the Basedow's disease A few patients showed the typical pattern of catatonia, as, for example, a 25 year old girl reported by Gause (2175), a 26 year old woman patient under Baylac's observation, a 31 year old female patient of Boiteau (1022) and a 37 year old female from Curschmann's clinic whose history Roper (1911) presents In the majority of the cases belonging here the mental condition remained unchanged or became worse. Four patients died Two have been discussed above, the other 2, a 25 year old girl reported by Gause, and a 37 year old woman described by Roper, became progressively weaker because of their refusal to take nourishment The latter patient also suffered from extensive pulmonary tuberculosis In half of the cases Basedow's disease appeared first and in the other half psychosis was already present when the signs of Basedow's diseases developed One patient was 19 years old, 4 were in the thirties, 4 in the forties and two in the fifties.

With exception of 2, all the cases in this group had a hereditary tendency

§156. Compulsion ideas, terrors and impulses are so plainly in evidence in many patients with Basedow's disease that one can speak of the compulsion psychosis We have mentioned that compulsive ideas can appear in the course of manic-depressive insanity and of melancholia

Thus, in the case of Peterson (733), there was kleptomania (see above), in that of Raymond and Serieux (1068) compulsive ideas and compulsive impulses were present

Those cases in which signs of compulsive psychosis were conspicuously developed had episodes of general restlessness, emotional excitement, a quarrelsome tendency or sad moods with extreme states of anxiety, tension and sleeplessness

Examples include the case of a 12 year old girl observed by Kronthal (1124), 3 female patients of Raymond and Serieux (1068), a 29 year old female described by Cohen (1027), and a 40 year old female under Baylac's observation (Faure 1305) Cohen's patient could not take a knife in her hand because she immediately felt *impelled to strike out with it* Baylac's and Raymond's and Serieux's patients had phobias, especially agoraphobia, as well as compulsive fixations Predominantly gloomy moods with anxiety states, sometimes with suicidal tendencies, were present in the case of Boiteau's (1022) 21 year old female, A Vigouroux's (1014) 22 year old

woman, a 27 year old female described by Schenk (938); a 32 year old woman described by Baumler (203), and a 42 year old female described by Solbrig (249) The last mentioned struggled with the illusion that she had to kill her children A woman patient of W G Thompson (2773), after prolonged sleeplessness, was burdened with murder and suicide impulses Because she was afraid she might yield to the impulse to kill her three children she entered the hospital. Cantonnet's (2364) 28 year old female patient with pronounced Basedow's disease had the compulsion of poisoning Among the patients of Schenk, Vigouroux and Boiteau were cases of anxiety.

The psychosis, together with Basedow's disease, was cured only in the case of the 42 year old female patient of Solbrig, and was improved in Vigouroux's case of the 22 year old girl, simultaneous with a corresponding improvement in the Basedow's disease In all other cases it remained unimproved, in Baumler's patient this was the case regardless of an improvement in the Basedow's disease.

The psychoses developed after a long course of Basedow s disease only in 2 patients (Solbrig and Baylac). In 2 cases they seemed to arise simultaneously: in the 12 year old boy observed by Kronthal and in the 27 year old woman whose case history Schenk described. In all other cases the mental *disturbance appeared first.*

It is noticeable that in this form of insanity all the patients, with one exception had a serious hereditary taint Only in the case of Solbrig's patient could this not be definitely established.

§157. Illusions of a paranoid type occur in a series of cases of Basedows' disease. In most of these, vivid hallucinations are so prominent that they can be described as hallucinationatory paranoia. It is hard to determine whether this concept is always fully justified In most cases there are visual hallucinations, or auditory hallucinations. Frequently both are present. A 24 year old man patient observed by Hirschl (2192) also had olfactory hallucinations. Diller's (2169) 46 year old female patient had olfactory and taste hallucinations. The content of the illusory images varied greatly.

Joffroy's (908) 25 year old female patient believed that she was threatened by a mad dog, Boinet's (1695) 27 year old female patient thought she was followed by thieves A 46 year old female with severe Basedow's disease observed by Diller (2169) believed she was lying in her coffin or that she had her dead child in bed with her In others the illusions had a predominantly religious content A 40 year old female patient described by Mannheim (1222) had a psychosis

In several of the cases belonging here, a flight of ideas, states of excitement alternating with anxiety and depression appear together with predominant moods of depression, activity compulsions or other characteristic illusions. These conditions we meet not infrequently also in Basedow's disease patients without pronounced psychosis.

This form of mental disturbance does not seem to show a definite predilection for certain age groups.

The cases in question are distributed between the ages of 24 and 50 The oldest patient, 68 years old, showed great restlessness, made repeated suicide attempts, and finally, before death from exhaustion, was definitely demented according to Pelman (997)

The psychosis was cured in only 4 cases a 28 year old woman in whom it appeared together with Basedow's disease after childbirth, a 31 year old man with conspicuous signs of a deterioration as reported by Kurella (985) and finally in the cases of 2 women, one of whom died from abscesses of both corneas

A very emaciated 36 year old woman came under my observation from the psychiatric clinic Basedow's disease had been present for 8 or 9 years After an unsuccessful partial goiter operation great restlessness appeared which increased to hallucinatory insanity In the further course an abscess of the cornea developed on the right eye and spread farther and farther After transfer to my clinic the destruction of the entire cornea could not be stopped Restlessness increased and the illusions of the patient were never absent When the first symptoms of panophthalmia appeared the *exenteratio bulbi* was performed Soon after, the woman became quieter Five weeks later she was mentally rational, her weight had increased and her general condition was improved In the case of a patient mentioned briefly by Mackenzie Davidson (1416) paranoia following abscess formation of both corneas disappeared during institutional treatment

In the other cases the psychosis showed little improvement or remained unaltered. Five patients died.

Arnaud's 47 year old patient as described by Boeteau (1022) had a chronic hallucinatory paranoia, death occurred suddenly without apparent cause By this time the symptoms of Basedow's disease had disappeared almost entirely Jessop's patient (1455) in whom the psychosis appeared, died soon after her admission to the asylum, the left eye had been enucleated and the remaining cornea had been largely destroyed by abscesses The 68 year old patient of Pelman (997) succumbed to increasing exhaustion. A 46 year old female with severe, rapidly developing Basedow's disease and acute hallucinatory insanity, as described by Diller (2169), died in coma A 47 year old Basedow's disease patient described by E Hounicke (2512) had a simultaneous osteomalacia which, to be sure, was only verified in the autopsy (see §219 below) The patient was always more or less excited and fearful He had illusions, hallucinations, and irrational ideas and suffered from sleeplessness With increasing weakness and great irregularity of the heart action he died 6 months after his admission to the Sonnenstein Asylum in Saxony

In all the cases belonging here except four, Basedow's disease was evident for some time, in some cases many years, when the psychosis developed In Render's (565) case both developed simultaneously at childbirth This woman had already recovered from an attack of puerperal insanity. In the

case of a 24 year old patient observed by Hirschl (2192), Basedow's disease with severe symptoms had appeared a few days before, and the acute hallucinatory psychosis two days before; Diller's (2169) above mentioned case *had* experienced an acute episode of Basedow's disease. A 40 year old male patient described by Slaven (2347) had paranoia for 3 years The Basedow's disease symptom complex was discovered during the examination

In all of the carefully described cases, with the exception of the acute disease in Diller's patient, more or less definite hereditary predisposition existed

§158. In 2 cases the psychosis in Basedow's disease patients appeared in the pattern of alcoholic insanity Both cases were women with a strong hereditary tendency.

Escat's 60 year old patient, as reported by Boeteau (1022), had had Basedow's disease for a long time When she took to heavy drinking, from the beginning of the climacteric, she gradually developed drunkard's delirium with alternating illusions and characteristic vivid hallucinations Later, there was loss of memory, dullness, loquacity and sometimes lively outbursts of emotion. The case of history of a woman contributed by Grohmann (1202) showed frequent indulgence in strong wines and use of morphine, the mental changes frequently observed in Basedow patients, and the vivid hallucinations characteristic of alcoholic delirium

G Carrier (2908) described a case of subacute alcoholic delirium in a patient who had a hereditary degenerative tendency and Basedow's disease for 4 years

§159. In cases of Basedow's disease ending in death, a mental disorder sometimes results which shows the pattern of acute insanity or *delirium acutum*. Also, in Basedow's disease patients with another form of mental disease, especially manic-depressive psychosis, the psychosis sometimes assumes this acute form before death (see §153 and §157).

In the 4 severe, acutely developing cases of Basedow's disease observed by Fr. Muller (1134) extreme excitement occurred which continued even when the patient lay exhausted Several complained of frightening dreams which continued even when awake, and they had vivid hallucinations These produced states of anxiety in the case of a 48 year old patient. In 3 of Muller's cases delirium occurred at the time that the illness became worse. At first there were remissions One patient was in the grip of fantasy ideas during these intervals. Finally the delirium became continuous. The state of stupefaction could no longer be interrupted by appeals. R. Brener's (1944) 43 year old female had acute insanity with anxiety hallucinations developed in the course of a very acute Basedow's disease 5 days before death.

A 51 year old patient from Curschmann's clinic, reported by Roper, (1911) displayed, during her acute Basedow's disease, continuously increasing restlessness with illusions One day before her death she was completely confused and lapsed into

a comatose state during which she died In the case of another patient from the same clinic, a 27 year old woman who had suffered Basedow's disease symptoms for several years, an acute exacerbation of the disease occurred during the third week of her confinement The nursing of her child weakened and exhausted her still more Eight days before death, and sixteen weeks after her delivery she became extremely restless and experienced sudden rises in temperature, complete mental confusion and violent jacktation Death occurred during acute delirium In Grohmann's (1202) 2 cases, a woman and a 62 year old man, restlessness and confusion came a short time before death The aforementioned case of Bruns (2268) was similar (see §129) above Pässler (2559) tells of the case of a 23 year old woman who had an acute exacerbation of Basedow's disease for a short time Violent excitement states alternated with anxiety attacks, visual hallucinations, and acute mental confusion Death came four hours after a goiter operation performed while she was in this state In several cases death occurred a short time after goiter operations due to Basedow's disease In each instance acute mental confusion amounting to delirium acutum had developed shortly before death

In the instance of a 51 year old greatly weakened and emaciated woman for whose case history we are indebted to Askanazy (1600) a similar mental confusion occurred Although there was no paralysis she could hardly be persuaded to sit up in bed Death followed one day after a partial goiter resection Here the mental disturbance probably had the significance of an exhaustion psychosis

There was no evidence of a hereditary tendency in any of Carrier's cases. Sometimes in the course of Basedow's disease milder forms of acute insanity arise and soon pass off.

Bruck (112) observed such a case, an 18 year old girl who, among other signs, displayed overactivity, loquacity and paraphrasia A 49 year old woman observed by Schultes (2230) showed the complete symptom complex of Basedow's disease The psychosis began with anxiety states and developed suddenly into acute confusion with hallucinations and irrational impulses With the administration of antithyroid serum a marked improvement in the symptoms of Basedow's disease and recovery from the mental disturbances resulted Zalplachta (2797) reports a 32 year old woman, who, during the course of Basedow's disease, suddenly developed anxiety states, great motor restlessness, visual illusions, dullness of perception, flight of ideas, speech confusion, complete disorientation, and sleeplessness After 5 months, parallel with an improvement in the somatic condition, a regression of the psychosis occurred

§160. A typical example of insanity of thyreogenous origin is provided by 1 case of Boinet (1820) and 2 cases of Parhon and Marbe (2724).

A 24 year old male without a hereditary tendency, observed by Bonet developed an acute thyroidism with motor and mental unrest following daily doses of 1 lamb's thyroid gland, a dosage later increased, against the doctor's orders, to 6 or 9 lamb's thyroid glands daily for a period of eight days This patient thought he was being followed, or taunted, ran about unclothed, refused food, became violent, threatened those about him, invented false tales, and showed himself to be completely irrational After withdrawal of the thyroid gland dosage slow improvement finally led to recovery When the man, a pharmacist, again ate 6 or 8 thyroid glands he relapsed into

the former condition Permanent recovery was achieved only when it was made im possible for him to obtain any more thyroid glands.

Parhon and Marke mention 2 cases in which the patients had taken large dosages of thyroid-gland preparations for therapeutic purposes and, as a result, developed psychoses which disappeared again when no more thyroid gland was allowed.

§161. After having reviewed the various forms of mental disturbances observed in patients with Basedow's disease, the question remains: are there any specific Basedow's disease psychoses? This answers itself, so to speak The great variety of mental ailments which may appear combined with this illness compels us to answer this question in the negative. Also, the individual psychoses by and large show no forms other than those which they otherwise display If we have to say, then, that there are no specific psychoses in Basedow's disease, I must still add emphatically, in order not to be misunderstood, that I am by no means of the opinion that it is a matter of an accidental combination of the two diseases in one individual. In a few cases, to be sure, another interpretation can not be excluded, that of a chance combination of both diseases in one individual with a hereditary neuropathic tendency. Examples are those cases in which the psychoses were present some time before the outbreak of Basedow's disease (see §154, §155, and §156) above, and probably, a few of those cases in which the signs of Basedow's disease were discovered during the examination of the mental conditions after transfer of the patients to institutional care. There are also cases in which alcoholism (see §158, above) or the puerperium (the case of Laehr 360 and Rendu 565, one case of Murray's 2553) actually were the precipitating factors of the psychoses

In the large majority of the cases we must, however, admit that Basedow's disease prepares the ground from which a mental disturbance arises more easily, in fact, in many cases one gains the definite impression that it imposes a definite pattern on the course of the psychosis and sometimes also influences the form in which it expresses itself.

In order that actual mental illness can break out in a sufferer from Basedow's disease another factor must, probably in the majority of the cases enter the picture, namely a hereditary neuropathic or psychopathic tendency. In the study of the various forms of mental disorder in Basedow's disease we have found almost without exception symptoms of mental degeneration in many forms: hallucinations, as in simple paranoia, compulsion manias as in dementia praecox. The large group of manic-depressive insanity and melancholy seems to comprise about 72% of the cases. A case described by Kocher (2197) shows very plainly that in persons having a predisposition Basedow's disease represents only one of the causal factors for the outbreak of the psychosis although it influences its course.

The melancholy moods of a 42 year old female Basedow's disease patient, the extreme anxiety and the excitement all disappeared following the operative treatment of the disease. Afterward, when the woman became somewhat run down because of a genital ailment, a mental disturbance again developed, although no Basedow's disease symptoms at all appeared

Certain observers in France went so far as to claim that Basedow's disease in itself was not able to bring about insanity in a normally constituted brain, and that in a person with a predisposition or mentally degenerated Basedow's disease represents only a chance cause, like any other, as for instance the puerperium, general or organic illness, mental shock, and the like They pointed out that Basedow's disease itself is a member of the large neuropathic family of diseases (Charcot) and a large number of patients with this disease show neuropathic or psychopathic antecedents On this foundation of nervous strain or mental degeneration not only the signs of Basedow's disease develop but also various other neuroses, neurasthenia, hysteria, epilepsy, and others, as well as insanity These various disturbances may occur simultaneously

In order to estimate correctly the relationship of the mental disturbance to Basedow's disease we must, above all, not forget that the mental changes occurring in these patients, as we have described so extensively above, display is most cases a quite distinct pattern which, in fact, can be called symptomatic for this disease Furthermore, the more developed forms of these disturbances cannot be distinguished sharply from the mildest forms of manic-depressive insanity.[1] The most frequent form of mental illness in Basedow's disease is just the one that bears the imprint of excitement, flight of ideas, activity compulsion or anxiety moods, inhibitions, pure mania, various patterns of states of manic-depressive insanity and melancholia. The latter occurs chiefly in advanced age The conviction forces itself upon us quite automatically, it seems, that the same poisons which produce the various symptoms of Basedow's disease also reach the portions of the cerebral cortex which determine the mental functions and damage them to a lesser or greater degree.

The intensity of the disturbance as well as the form in which it displays itself may well depend in part, indeed, upon the quantitative and qualitative differences in these poisons and upon the shorter or longer duration of their action, but chiefly upon the individual traits, especially developed under the influence of the heredity, upon the varying susceptibility with which this or that complex of centers is subjected to harmful influences. We know, in fact, concerning various poisons that one and the same substance can produce mental illness of various forms according to the strength of its action and the general momentary disposition of the individual affected So we see, for instance, under the influence of alcohol, in one person

[1] Rogers (2429), physician at the Milwaukee Sanatorium, says that in his experience manic symptoms are to be found in Basedow's disease in three-fourths of all cases of psychosis

one sign of excitement, uncontrolled hilarity, talkativeness and compulsions of argumentativeness and a quarrelsome tendency, while we notice in another inhibitions, emotionalism, weeping moods, or sleeplessness One state can pass over into another The various forms of mental disturbances following sulfur poisoning, from the slightest degree up to pronounced complex psychoses show analogous relationships[1].

The milder forms of mental disturbance in Basedow's disease are observed in individuals in whom no hereditary tendency can be recognized, and who, up to the time of the outbreak, have shown no signs of any special predisposition. Although Hirschl (1208), to be sure, claims that a high degree of irritability is a *signum degenerationis*, he is mistaken. This unusual irritability is an especially frequent characteristic of the mental change produced by the Basedow's disease poisons This, as we have emphasized above (§149 and §150) becomes apparent with the appearance of the disease, and sometimes, in fact, is the first symptom in individuals who previously had shown calmness and good sense.

Gause (2175) must be emphatically contradicted when he allows himself to assert that the questionable character of Basedow's views on the nature of the disease is appa [illegible] and [illegible] dow [illegible] in in [illegible] actually fits only a limited number of cases, as we have seen above

A closer relationship of Basedow's disease to the psychoses is indicated by the cases in which both run parallel to a certain degree. With an exacerbation of Basedow's disease the psychosis also assumes a more severe form, or an already existing mental disturbance obviously is influenced unfavorably Finally, there are a few cases in which, with an improvement or cure of the Basedow's disease the psychosis also disappeared Examples are presented for all of these eventualities among the cases described above. These could be duplicated extensively It is probable that in some isolated cases mental disturbances observed prior to the diagnosis of Basedow's disease were actually no more than the first evidence in an individual of a psychopathic tendency susceptible to the action of the toxin which produces Basedow's disease

As a characteristic example I would like to call attention to the case history of a young man described by Landouzy (717) who called attention to the forensic significance of such cases A nervous 25 year old male had a tendency to outbursts of temper dating from childhood After he became a soldier there were frequent outbursts of

[1] See especially Laudenheimer Die Schefelkohlenstoffvergiftung der Gummiarbeiter, u s w , Leipzig, 1899, and F Quensel, Monatsschr f. Psychiat u Neurol. XVI, S. 48

anger which amounted to such states of fury that he often had to be severely disciplined for insubordination When he was finally brought to the hospital the signs of Basedow's disease were recognized Perhaps a similar interpretation is permissible in the cases of Impacciant and J Faure (see §153 above) both of which involved young women with psychopathic tendencies and a melancholy mood for a brief interval before the appearance of signs of Basedow's disease In Impacciant's case it would be hard to decide the extent to which pneumonia (see §153 above) influenced the outbreak of the disease

In many cases of compulsion psychosis and hallucinatory paranoia, and even in alcoholic delirium, an influence of Basedow's disease on the psychosis is apparent. The compulsive ideas and impulses, the illusions of paranoia, and the characteristic symptoms of alcoholic hallucinations are accompanied by more or less distinct signs of general unrest, excitement, flight of ideas, or anxiety. (see §156 and §157)

Finally, there is a series of severe or fatal cases in which the psychoses became evident in the form of acute confusion or delirium in the course of Basedow's disease, usually just before death. This also occurred among individuals in whom a psychopathic tendency could not be demonstrated (see §159 above).

The form of these mental disturbances corresponds completely with the disease picture of the toxic and infectious psychoses to which that of an exhaustion psychosis is directly related According to our present views, these have to be distinguished etiologically. In all these forms the decisive factor is the damaging action of toxic agents on the cerebral cortex. Although varying in details, the following are common to all: disorientation, complete incoherency of ideas in wild flight, sensory illusions up to and including clouded consciousness, deep introspection, muttering delirium, exaggerated activity *compulsions with unorganized motor impulses up to and* including jactation. The cases described above (§160) of intoxication psychoses following excessive intake of thyroid glands must really be considered an experiment, although in these patients a special individual predisposition must be assumed in order that the misuse of thyroid glands could produce such severe manifestations With the exception of the eye signs they present the complete pattern of an acute Basedow's disease *Nevertheless, a conspicious psychopathic tendency was absent.*

§162. We shall now take up a series of Basedow's disease signs which are to be attributed to a disturbance in vasomotor and secretory innervation

Vasomotor Disturbances

§163. A manifestation very frequently observed in Basedow's disease is a tendency to blushing after slight mental or physical excitement. This

reddening confines itself to the face, but sometimes extends over a large part of the body surfaces.

Rummel (935, 9th case) reports a 19 year old female patient with this disease who exhibited erythema spread over the entire thorax when undressing Variot (2132) observed in the case of a 4½ year old girl. upon slight cause, as for instance the taking of a rectal temperature, a sudden spreading scarlatiniform blush of the whole integument occurred

The characteristic tendency of Basedow's disease patients to blush suddenly was observed very early, as for example by J Begbre (52), Fletcher (134), Creadle (223), Stellwag (235), Chvostek (369), Shapley (321), Roesner (340), Johnstone (593), Lewin (777) and many others

Momentary blushing without definite cause, confined to face, neck, and upper breast region is not unusual in Basedow's disease patients Sometimes the reddened regions feel warmer and a localized rise in temperature can be demonstrated with a thermometer

In some cases only one side of the face becomes reddened.

This is illustrated in the case of v Stellwag's 23 year old female patient Without any special cause the left side of the face would redden while the right side retained its usual color But when she was mentally stimulated both cheeks would become bright red and a fine meshwork of bright superficial blood vessels became visible to the naked eye

In the case of a 27 year old female reported by Ph Schulz (320) the right cheek became intensely red under excitement A temperature rise of 1° above that of the left cheek could be demonstrated

In more infrequent cases only circumscribed parts, such as the ears, are the areas of reddening and of a rise in temperature.

In the case of a 3½ year old child with Basedow's disease Demme (401) observed an outbreak of perspiration on the right side of the face, a reddening of the right external ear and a temperature increase of 05° to 0 7° in the right external ear canal above that of the other side Chvostek (393) described a 12 year old girl whose ears, sometimes one, sometimes the other, sometimes both together, became deep red without special cause for different lengths of time up to 1 hour

More rarely the redness occurs in a spotty pattern

Gerhardt (1105) observed the signs of a patchy redness about the mouth and cheeks during states of excitement in the case of a 32 year old female with severe Basedow's disease Baumblatt (422) saw a patchy redness appear on the thorax of a 32 year o
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of the face Chevalier (884) saw erythematous patches over the upper thorax in an acute fatal case of a 30 year old man

In 10 of W. G Thompson's (2773) 80 cases erythemas were present. Often they appeared localized. In the case of a 32 year old woman observed by L Humphry

(2518) an erythema appeared on the legs and back shortly before death In 2 cases among 18 reported by Hunerfauth (1735) a fleeting erythema occurred In 1 patient among Kocher's (2197) numerous cases large reddening patches appeared on the breast and neck

§164. The skin color of a large majority of patients with Basedow's disease is pale and sallow. However, the face often appears steadily bright red and full, an appearance in striking contrast to the rest of the body. Sometimes the reddened skin is filled with a coarse network of enlarged veins. (Romberg and Henoch 39, Geigel 181; Trousseau 219, v Stellwag 235, Cheadle 223, 9th case, and 331, 7th case, Sollo 864, a soldier, covering face neck and chest, and many others).

In isolated cases only half of the face became reddened and warmer and the exophthalmia and lid signs occurred only on the corresponding side In a few other cases, together with the reddening of the face, other unmistakable signs of paralysis of the homolateral cervical *sympathicus* were observed.

In the case of a 24 year old female patient of Percy Fridenberg (1308), exophthalmia *and lid signs were present on only the left The left half of the face appeared* red under the slightest mental excitement This contrast became more striking when she blushed

Chvostek (269, 15th observation) in the case of a 55 year old woman noted a right-sided swelling of the thyroid gland, a slight protrusion of the right eye, a bright reddening of the right half of the face, and perspiration on the right side

In the case of a 19 year old woman for whose case history I am indebted to Samelsohn, the right eye had protruded for a long time The right side of the face was bright *red and direct measurement demonstrated higher temperature The pupils of the* eye were not unequal

In the following cases a complication by *sympathicus* paralysis could not be overlooked Chvostek (269) observed such a case involving a 20 year old man Besides marked reddening and warmth of the right half of the face and a rightsided hyperhidrosis the right pupil was smaller than the left and the right palpebral fissure was relatively narrow Exophthalmia and lid signs were absent Jacobsohn (1739) reported the case of a 38 year old female patient with Basedow's disease and a long-standing *hemicrania (see §139 above) First the left and then the right half of the face became* reddened and somewhat moist, when the right half became red, the left remained pale and entirely dry This difference stood out even more distinctly when the patient *became heated or inwardly excited Then the right half of the face appeared as if* flooded with a glow Furthermore, the left pupil was about half the size of the right The left palpebral fissure was small not simply because of a lower position of the upper lid but also because of an upward shift of the lower lid The left eyeball lay somewhat deeper in the orbit, although there was no actual protrusion of the right one (see §68 *above) There were, in this case, beside a vasomotor paralysis of the right side of the* face, well defined signs of a left *sympathicus* paralysis involving fibres arising in the pupillary nuclei as well as the sweat gland fibres which join the sympathetic trunk at about the same point On the other hand, there was no paralysis of the vaso constrictor fibres of this side If one does not, in agreement with the author, wish to as-

sume a perpetual state of stimulation of these fibres, one can think of it as a paralysis of the vasodilators

In a case of Basedow's disease presented by Eulenburg (226) the pallor and lowering of temperature of the right half of the face probably can be attributed to a complicated state of stimulation of the cervical *sympathicus* of the right side, since the right pupil was found to be larger and the right palpebral fissure was wider (see §68 above) Inequality of temperature between the two halves of the body, with a difference of from 0.1° to 0 7° was found by Gluzinski (468) in 4 of his 15 cases, the higher temperature was on the right three times, and on the left once Whether any signs of a *sympathicus* involvement existed cannot be ascertained

Abnormal pallor and coolness of the skin, sometimes combined with a feeling of itching in the parts involved, for instance the fingertips, may follow a transitory, localized spasm of the small vessels Such a local asphyxia has been observed in patients with Basedow's disease only very exceptionally (see §218 below).

§165. An annoying sensation of heat in face, neck and chest is a very frequent early symptom of Basedow's disease. Sometimes these parts are vividly reddened, frequently there is also increased perspiration (see §168 below) The feeling of warmth is quite independent of the season or outer temperature Often it occurs only temporarily and sometimes only at night In other cases it is lasting but of varying intensity It can disappear again in the course of the disease Exceptionally, it may even reverse itself (see below) It is characteristic for these patients that they seek coolness and breezes, like to have neck and chest uncovered, wear thin clothing even in winter, throw off the blankets at night, cannot lie quietly, splash head and chest with cold water as often as possible, and demand cold beverages or ice (thermophobia). Sometimes they complain of a burning sensation in the mouth or throat.

In his first observations v Basedow (15) has already described this peculiarity in vivid terms Later he especially emphasized it in additional cases, as have Beigel (181), Bäumler (23) especially in the palms of the hands, von Teissier (146), Charcot (in several places), Trousseau (219), Fournier and Oliver (190), as well as Fennick (302), Hutchinson (312), Lander, Brunton (320), Baumblatt (422), Chevalier (882), Kronthal (1124), Fr. Muller (1134), Buschan (1181), Murray (2213) and others

In the case of Budde's (879) 53 year old female patient the disease began in her fiftieth year with a sense of a burning heat throughout the whole body, reddening of the skin, and itching, but no excessive perspiring. Cardiac palpitation became violent in attacks which returned every 15 minutes and lasted several minutes.

H Mackenzie (918) noted sensations of heat or hot flushes 13 times among his more than 30 cases, Mannheim (1222) 24 times among 51 polyclinic patients A local rise in temperature was demonstrated only in a few instances Many of Kocher's (2197) numerous patients with Basedow's disease complained of strong sensations of heat. All except one perspired freely In this one case there was no abnormal perspiration, but strong sensations of heat were present. In the case of a 30 year old fe-

made a sensation of great heat alternated with sudden chills, perspiration, however, continued through both periods. A rise in temperature could not be objectively determined in either case Kroug (2700) noted the manifestation of thermophobia in more than half of his patients with Basedow's disease

Variot (2132) mentioned the sensation of torturing heat in the case of a child with this disease, a 1½ year old girl who threw off the covers at night even in winter Perspiration was not notably increased Cohen (1031), from among 16 of his cases at the Mendel Polyclinic, mentions three in which an amnesia showed troublesome sensations of heat and much perspiration At the time of the examination, however, they complained of a freezing chill A female patient of Baylac (1305) was troubled by a morbid feeling of chilliness during periods of local perspiration

§166. Hemorrhages from mucus-membranes are to be itemized next. They are probably due in part to an angioneurotic disturbance which is by no means a rare occurrence in Basedow's disease The most common is *epistaxis, but hemorrhage from the stomach, intestine, lungs or uterus has been observed several times, without evidence, by the examination methods* at our disposal, of other pathological changes in the organs under consideration These hemorrhages can sometimes reach a degree which causes anxiety They last a while and stop again by themselves. Sometimes they arise at the time of exacerbation of other disease symptoms In a few cases the bleeding accompanied the first symptoms of Basedow's disease

Violent epistaxis in patients with Basedow's disease is reported by Trousseau (219), Cheadle (223) and W Begbie (295), Benedict mentions it 3 times among 7 cases, S West (686) once among 38, H Mackenzie (918) 7 times among about 30 cases, Ditisheim (1293) 3 times among 17 patients, J A Hirschl (2193) once among 14 cases, Kocher (2197) 7 times among 80 cases (1 time also bleeding of the gums), W G Thompson (2773) 1 time among 8, and K Schultze (2749) 7 times among 50 cases In one of the 95 patients observed by myself, a 19 year old girl with severe Basedow's disease, a voluminous nosebleed occurred after the disease had been present for about 3 months, this continued with remissions for more than three months, although the general condition improved at the same time

In 2 among 6 cases described by Popoff (1899) bleeding was a conspicuous symptom in the course of the disease There were frequent nosebleeds and hemorrhages from the uterus A local examination could not demonstrate any abnormal condition of the genital organs *The gums also bled and a few superficial bleeding cracks occurred about the lips Furthermore, there were occasional unexplained massive extravasations of blood into the skin of the extremities Following improvement in the Basedow's disease the bleeding ceased entirely* A 27 year old woman with Basedow's *disease, but no exophthalmia, had hemorrhages from the nose, throat, rectum and uterus* Several uterine curettages brought no lasting improvement *In a third case* bleeding played only an unimportant role

In Trousseau's case (219) of a young lady, Basedow's disease started with a nosebleed which continued intermittently for six weeks Amenorrhea began at the same time In the further course frequent voluminous nosebleeds occurred These hemorrhages which were often dangerous in amount seemed to put an end to the acute exacerbations of the disease After each there was an apparent remission In the case of S West (686) cardiac palpitations and frequent nosebleeds preceded the outbreak

of the disease In the case of a 50 year old woman, described by Jeanselme (1213), daily epistaxis and headache accompanied the development of other symptoms Exophthalmia and lid signs were absent Mackenzie (918) observed epistaxis at the beginning of the disease A 50 year old female described by Jeanselme (1213) had daily nosebleeds and headaches accompanying the development of the symptoms of Basedow's disease Spontaneous epistaxis occurred up to five times a day as the first noticeable manifestation in the case of a 21 year old female patient of Garre (H Moses 2864) One month later an enlargement of the thyroid gland became evident Five months later the eyes protruded further and still other signs of the disease appeared which were attributed to a great shock

In Popoff's (see above) second case the disease started with uterine bleeding Menorrhagias were also observed by Revilliod (1373) and Murray (2213) in 1 case each

Cases of hemoptysis are reported by v. Graefe (63 and 192), Friedreich (191), A Maude (1057) in a 40 year old woman, Kocher (2197) in a 41 year old woman, G

tuberculosis

In 1 case of Graves (18) the disease began with profuse, bloody diarrhea J. Begbie (29) mentioned the loss of 5 or 6 ounces of blood from the rectum in the initial stage of the illness Maude's above-mentioned female patient also had hematemesis and melena In a severe case of Basedow's disease reported by Thorbecke (2589) a 28 year old woman suffered from profuse watery diarrhoea, bloody stools, and hematemesis shortly before death At the autopsy no defects of the mucous membranes of stomach or intestine were discernible

Hematemesis is mentioned by V Oppolzer (184), Mannheim (1222) in the case of a 32 year old woman, and Revilliod (1373) in that of a 40 year old female patient with Basedow's disease

The occurrence of extensive bleeding from the skin may be designated as quite an unusual manifestation. In addition to the case of Popoff (1899) already described above, Revilliod (1373) reports cutaneous hemorrhages in the fatal case of a 38 year old female; J Rogers (2736) describes exchymotic spots on various parts of the body surface in the case of a 29 year old woman with a very severe form of Basedow's disease. The occurrence of purpuric spots in Basedow's disease has been described by several observers, including Joffroy (1117), Dore (1955), Ulrich (2028), Variot and Roy (2132) and M. V. Ball (2453)

In Dore's case red painful swellings appeared on one leg and over the epigastrium Later tiny ecchymoses appeared on these places In the case of a 45 year old woman observed by Ulrich, purpura appeared on the legs after three years of the fully developed disease and accompanying the first myxedematous symptoms (see §224 below) Variot and P Roy saw in the case of the above-mentioned 4½ year old girl several purpuric spots on the lower and upper extremities In Ball's case numerous purpuric spots appeared on the extremities of a 24 year old woman a few days before her death.

The absence of objectively demonstrable disease in the respective mucous membranes and organs, as well as the irregular occurrence of the bleeding, indicates an angioneurotic origin. An intense local congestion under the influence of the increased heart action of patients with Basedow's disease produces a tendency to bleeding Yet the assumption of a transitory local injury to the vascular walls by a toxic material in the blood can not be cast aside. Many infectious diseases and certain intoxications give rise to a tendency to localized bleeding.

§167. Among the signs of a disturbed innervation of the smaller blood vessels, one is to be noted which indeed is not pathognomonic for Basedow's disease But if one looks for it, it will often be found in those afflicted with this disease, the so-called urticaria or *taches cérébrales*, as Trousseau (166) calls it in the first description of this manifestation. If one rubs over the hand with a hard object such as a fingernail or a metal probe, he observes in about two seconds a reddening of the skin corresponding exactly to the place stimulated, and lasting for several minutes or longer Sometimes weals form in this area, it is then called *urticaria factitia* The observation has been made, and expressly emphasized, that such demographism can no longer be produced after improvement or cure of Basedow's disease.

Following Trousseau's observation this sign has been noted in the reports of Paul (174), Peter (175), v Dusch (207), Cheadle (223), Chvostek (224) 4 and 5 *observations, Roesner (340, 1st and second observations), Benedikt (348) in 2 of 7* cases, Schöenfeld (504), Merklen (494) in the case of a 27 year old female during an acute exacerbation of the disease, by Chevalier (882) in another very acute case, by Lewin (777) 9 times among 22 carefully annotated cases, by Joseph (909), Schenk (935), Volkel (945), by Cohen (1031) 4 times among 16 cases, by Barella (1171), Risley (1375), le Clere (2093), Diwanin (2170) 2 times among 4 cases, and by J A Hirschl (2192) 2 times among 14 cases Kocher (2197) saw dermographia only once in pronounced form among his numerous cases, Riedel (K Schultze 2749) saw it only once among 50 patients with Basedow's disease G V Voss (2352) and Dreschfeld (2485) mention it in several cases and Fujisawa (1965) mentions it in a 53 year old female patient at the Munich medical clinic An unusually fine observation of this kind is given by Ulrich with the addition of a good illustration

A lasting hyperemia, produced by slight stimulation of the skin was observed by v Leube (1127) in the case of a patient with this disease

The signs in question have often been observed also in children with Basedow's disease

Steiner (1512) observed pronounced dermographia in the case of an 8 year old girl, a 9 year old girl and a 12 year old girl Zuber (2036) observed it in the case of a 13 year old girl and Bootz (694) in that of a 14 year old boy who had severe Basedow's disease The manifestation disappeared with the improvement of the other symptoms Brower (1699) observed dermographia in 4 children (siblings) with Basedow's disease

Peyron and Noir (1235) produced *urticaria factitia* by the flying sparks of an electric machine sprayed upon the skin. Where the sparks hit a white point appeared somewhat raised above the surface, and after half a minute a red zone surrounding it appeared Various patterns could thus be drawn on the skin, lasting four or five minutes. Among 30 other patients studied in this way none of whom showed any signs of Basedow's disease, this phenomenon could not be produced Dermographia could be produced in patients with this disease by ordinary mechanical stimulation Following *galvanic treatment the symptoms of Basedow's* disease improved as this peculiar susceptibility of the skin diminished.

The absence of demographia in their patients was especially noted by a few observers (Pulitzer 217, Chvostek 252, observations 8, 9, and 10, Raynaud 338, 3 observations, Boettger 375, Savage 568, Schenk 938).

Later we shall deal with other forms of angioneuroses of the skin in connection with the various pathological manifestations on the skin of Basedow patients (see §193 below).

Abnormalities of Perspiration

§168. One of the most frequent signs of Basedow's disease is an increased perspiration It often appears among the first symptoms. Many patients state quite definitely that they had perspired easily and continuously only since the beginning of their illness. Like so many signs of this disease, this too varies in intensity In many cases, the skin, especially that of the hands, feels moist all of the time In many patients slight bodily movement or the slightest mental excitement is sufficient to produce profuse perspiration, as, for example, in the case of a 30 year old female patient of Kahler (766a) who perspired even after feeling the small prick with a needle Perspiration often occurs in areas which do not usually perspire under such circumstances Many patients perspire so heavily, for instance, that they have to change their linen several times during the night. Many are continually bathed in sweat Even in winter such patients perspire so much that "the body is actually odorous", as P Marie (555 p 42) has seen repeatedly. Outbreaks of perspiration can also be localized in the palms of the hands or the face We have already mentioned that tachycardia attacks may also be accompanied by localized outbreaks of perspiration (§5). In exceptional cases very malodorous perspiration can be secreted

Thus v. Basedow reports stinking night-sweats in the case of a young woman with the typical disease Dauscher (820) mentioned a "thoroughly ill-smelling" perspiration in the case of a 32 year old female patient

A circumscribed eruption of miliaria can appear on the sweating areas, as J. Nevins Hyde (2209) has observed in one case. But this is certainly not striking.

All 16 cases of Basedow's disease which Cohen (1031) assembled from Mendel's polyclinic, showed a more or less pronounced hyperidrosis In 3 cases it was, to be sure, no longer evident at the time of the demonstration (see §165 above) Among the 47 Mendel patients reported in the following years Mannheim (1222) included 27 who suffered from hyperidrosis Among Passler's (1362) 51 polyclinic patients 29 complained of excessive sweating Local hyperidrosis was noted in hands, feet, head and axillae, and once only in the stomach region Among Kocher's (2197) 80 cases increased perspiration was mentioned in 70, in 36 of these it was abundant or extremely profuse, and in 34 moderate In 4 cases it was specifically mentioned that the skin did not perspire, and felt dry instead In 113 of Murray's (2553) 180 cases the skin was always moist, and in 92 of these perspiration was profuse An abnormal tendency to perspiration was present in 18 among 50 bases of Basedow's disease from the surgical clinic of Riedel (K Schultze 2740), and in 25 of 46 cases from Strumpell's clinic (Donelan 2644) Among 106 cases observed by Kroug (2700) profuse sweating is noted in 89 Thirty patients under Frank Billing's observation (2806) sweated profusely, among 20 others sweat secretion was not disturbed and 2 had a strikingly dry skin (see below) Among 62 which I, myself, observed definite histories of hyperidrosis are given Fifty of these patients perspired quite profusely, a few of them mainly at night In the histories of 12 cases it is mentioned that they did not perspire more than usual, a few of these complained of hot flushes One patient had chilly sensations and cold sweats

It happens rather rarely that patients with Basedow's disease perspire more on one side than on the other or that the hyperidrosis is entirely confined to one side

Nitzelnadel (196, p 47) briefly describes the case of a 47 year old man who had the *usual symptoms of Basedow's disease, a leftsided headache, a left pupil smaller than* the right (see §68 above), and more perspiration on the left half of the face than on the right Chvostek (269) observed a vigorous 20 year old soldier with incompletely *developed Basedow's disease Exophthalmia and lid signs were absent There* was a marked reddening of the right side of the face, and profuse perspiration on the right side of the face and body The right pupil was narrower than the left, and the *right upper eyelid rested lower than the left (see §68 above) The temperature in the* right axilla was 37 3° against 36 8° in the left, and in the right cheek 36 8° as compared with 35 6° in the left The pulse rate was 108 to 124 per minute A chiefly *rightsided hyperidrosis preceded the development of the other Basedow's disease* signs by about two years

In the case of a 55 year old woman, described by the same author (269, 15th observation), there was in addition to a rightsided enlargement of the thyroid gland, a slight protrusion of the right eye, and a hyperidrosis with reddening of the skin on the right side E Fraenkel (305) reports a 60 year old male with moderate tachycardia, marked palpitations, rapid carotid pulsation, large sub-sternal goiter, and unusually profuse perspiration entirely confined to the left side When the patient *did not exert* himself he perspired only about the head, the slightest effort, however, caused perspiration to cover the whole upper half of the body, particularly the head *Intermittent dyspnea was always combined with a sensation of heat and leftsided sweating* Furthermore, the right pupil appeared smaller than the left and the right palpebral fissure was narrow (see §68 above) The autopsy showed changes in the ganglia of the left sympathetic chain *We have already referred (§164) to Jacobson's (1739)* case with

sweating only on the right side of the face, pallor with dryness on the other, with narrowing of the left pupil and left palpebral fissure Schulz's (320) 27 year old female patient had conspicuous redness of the right cheek Perspiration was confined to the right side, under excitement the temperature of the much reddened right cheek was 1° higher than that on the left A 3½ year old child observed by Demme (401) displayed marked reddening of the right outer ear and rightsided perspiration of the face

Eckervogt (516) reports a 22 year old woman whose entire face reddened She felt more moist and perspired considerably more on the left than on the right A 32 year old female patient of J Russell (567) suffered from outbreaks of unilateral perspiration so intense that she had to wipe it off constantly Lewin (777) reports a 36 year old female patient with Basedow's disease whose face was warmer on the right side than on the left The perspiration on the right side was more profuse than that on the left The right pupil was larger than the left Also, M J Taylor (794) described a case with unilateral perspiration. Runge (2228) reports a case from the Ebstein clinic, a 19 year old girl with a moderately large, soft, symmetrical goiter The left eyeball protruded more than the right, and over the left half of the face, especially the upper lip, an abundant, extremely sour sweat was secreted In one of Passler's (1362) patients, perspiration occurred unilaterally, first on the right, then on the left

In the 3 cases showing a unilateral hyperidrosis in Basedow's disease definite signs of a paralysis of the cervical *sympathicus* on the perspiring side were present (Nitzelnadel, Chvostek and Lewin) In Fraenkel's case we probably have to assume a stimulation of the oculo-pupillary fibers on the side of the profuse perspiration (see §68 above) and in Jacobson's case signs of a paralysis of the fibers arising in the oculopupillary center of the opposite side were evident

Sweat secretion is independent of the state of distention of the blood vessels of the respective region as has long been known. Likewise, there remains scarcely any doubt that the sweat-stimulating fibers in the peripheral nerves and for the head, the trigeminal and facial nerves, are directed toward the skin There is still a question as to how many of these take a direct course from the sweat center and how many pass through the *sympathicus*. Experimental evidence, as well as clinical observation, seems to indicate that large individual differences exist here, at least for the face, with respect to frenosudoral and excidosudoral fibers; these enter the trunk of the *sympathicus* in varying numbers From there they pass to the skin by detours (Higier, H Schlesinger). However that may be, the hyperidrosis in patients with Basedow's disease is probably to be attributed to a toxic stimulus acting on the perspiration center.

A quite exceptional occurrence in Basedow's disease is an extreme pallor and dryness of the skin sometimes combined with chilly sensations.

Chvostek (400) reported such a case, a 46 year old man who had not perspired anymore following the onset of Basedow's disease and who had a sallow, dry skin Cohen's (1031) three cases belonging here have been mentioned above (§165). Among Kocher's (2197) numerous cases, it is reported about four times that the skin never perspired, but instead felt dry In one of these an exfoliation occurred on the extensor side of the extremities Among all these cases none had indications of myxedema (see §221

below) In the case of Beltman's (1406) 54 year old patient the sweating ceased as a complication at the appearance of diabetes after eight years of Basedow's disease The skin was entirely dry, wrinkled, and stiff The hands were usually burning hot. Upon the occasion of a temporary improvement the patient had definite perspiration for a few days

§169. In close association with the increased tendency of Basedow's disease patients to perspire another sign occurs. This is presented in the literature as Vigouroux's sign, a reduction of skin resistance to electricity

Chvostek (221 and 252) emphasized that Basedow's disease patients were extremely sensitive to relatively weak currents, and that this sensitivity diminished with progressive improvement. In 1885 Charcot (613 and 652), in a clinical lecture, called attention to the sign first noticed by his pupil Romain Vigouroux He emphasized its importance for the diagnosis of incompletely developed forms of Basedow's disease. R. Vigouroux (740, 1 and 798) in 1887 and again in 1888 made the statement that patients suffering from Basedow's disease show an extremely low resistance to the passage of a galvanic current. This reduction in electrical resistance was then more precisely designated by Eulenburg (708 and 825) and Kahler (1775a) as an accelerated lowering of resistance to conduction and a reduction of the relative resistance threshold

This property is more exactly expressed as follows: 1. The absolute minimum of skin conduction of electric currents—that is the irreducible minimum below which no more electrical conduction occurs—is lower than in healthy persons, or in those with other diseases 2 The relative resistance minimum, that is the lowest point at which a definite relatively slight flow of current is attained, is exceptionally low, and is reached much more quickly Steppetat added his observation (914) that the initial resistance of the skin to penetration by galvanic current, measured by Jolly's method with precautions against error, gave much lower values than in other persons In rare individuals not afflicted with Basedow's disease an initial resistance as low as that of those who are so afflicted can be demonstrated But the opposite does not seem to occur in patients with Basedow's disease

These observations very soon were confirmed by other investigators including Martius (725), R N Wolfenden (744), Silva and Pescarolo (865), von Seglas (940), Cardew (958) and others. It became evident that the sign cannot be considered pathognomic in any way and also, that it is not as constant as Vigouroux and other French doctors assumed Most observers admit, however, that it appears very frequently and often early in Basedow's disease patients In doubtful cases it can probably have diagnostic importance, although its absence would not speak against Basedow's disease if the diagnosis is otherwise supported sufficiently

Seglas (940) states that, in the case of a 27 year old female with melancholia, tachycardia and slight exophthalmia, but no goiter, a correct diagnosis was reached by way of the electrical skin resistance test Among 8 other melancholias the resistance was much higher He pointed out that in these cases the skin was pale and dry

Martius (725) denied that the absolute threshold has diagnostic value, since this value in Basedow's disease differs little from that among well persons or those with other diseases. The relative resistance threshold, although it is often lower than that among the well, is not invariably specific for Basedow's disease Chardew (958) also rejected the diagnostic significance of this sign on the basis that it occurs only in patients who perspire appreciably or anyone else whose skin is moist. Special equipment is not really needed to demonstrate such a tendency toward sweating To a large extent all this is correct Vigoroux contends that loss of electrical resistance in the skin reflects the condition of the vasomotor innervation, and regards this test as the best index to the state of the vasomotor system Eulenberd and Martius attach importance to the fineness of the skin and the distention of the skin vessels resulting from vasomotor instability. According to my own findings it can no longer be questioned in this day that the phenomenon results from an increased moistening of the outer skin with a salt solution which bathes the cells and pores and acts as a good conductor between the body and the electrodes

It is not an effect of actual sweating, for that was especially avoided in the investigation; a greater moistening of the skin by *perspiratio insensibilis* was sufficient.

Ditisheim (1293) especially emphasized, in the case of a 21 year old female patient with Basedow's disease, that the conductivity resistance of the skin to electric current was greatly reduced, although the skin felt quite dry

In a Basedow case complicated by diabetes, a 54 year old female reported by Bettman (1406), the electric conductivity resistance was distinctly lowered in spite of marked dryness of the skin

Sollier (1005) observed 2 cases of Basedow's disease without goiter and with a swelling of myxedematous character extending over the entire body On the limbs, especially, the swelling had a hard consistency, in the second case, a 39 year old woman, the appearance was reminiscent of scleroderma The skin was dry and no perspiration was perceptible Nevertheless, conductivity resistance of the skin was distinctly reduced Along with improvement of the whole picture—the pulse rate reduced to 90, exophthalmia no longer noticeable, and the peculiar edema very considerably reduced—conductivity resistance of the skin to electrical stimulation increased (see §221 below).

Kahler's (775a) experiments demonstrated that distention of the blood vessels of the skin alone cannot produce the phenomenon. After transection of the *sympathicus* or after inhalation of amyl nitrite the resulting hyperemia of a shaved rabbit ear did not have the slightest effect on the conduc-

tivity resistance. Donath (840), to be sure, found a slight reduction in the conductivity resistance of the skin after section of the cervical *sympathicus* for epilepsy in the case of a 38 year old woman. This is, however, as he himself suggested, to be attributed to an increased sweat secretion probably resulting from a loss of the frenosudoral nerve fibers.

Among patients with Basedow's disease a relatively large deflection of the galvanometer needle with a low electromotive force occurs immediately after the closing of the circuit; the characteristic slight reduction in resistance develops after a few seconds, this teaches us that it is not the frequent reddening at the application points of the electrode, which occurs in these patients easily, which is responsible *for this manifestation*, but that responsibility for it rests exclusively on the physical or cataphoretic action of the current. Even in healthy persons a moist state of the skin, especially *after* subcutaneous injection of pilocarpin, reduces the conduction resistance of the skin. This is to be expected from the reports and was confirmed by the experiments of Kahler and other investigators. As we have seen, increased perspiration is remarkably frequent in patients with Basedow's disease. The reduction of conduction resistance follows easily *even when no appreciable secretion of sweat can be perceived*. The test of conduction resistance by galvanic stimulation of the body offers an enlargement and addition to the symptomology of Basedow's disease whose value should not be underestimated.

Vigouroux considered the sign valuable for differential diagnosis, especially in hysteria. But he was probably in error. He believed (798) that when the electrical conductivity of the skin was not lowered in patients with Basedow's disease it indicated a complication by hysteria. Soon afterward Silva and Pescarolo (865) showed that an elevation of the conduction resistance in the skin was by no means a constant finding in hysterical persons. Perregaux (1233) found the electrical conductivity resistance of the skin distinctly reduced in the case of a 19 year old male Basedow's disease patient with pronounced hysteria.

Symptoms Involving the Digestive System

§170. Disturbances of the digestive system play an important role *among the symptoms of Basedow's disease not only because of the frequency* of their occurrence but also because of their extensive influence on the course of the illness.

§171. Lack of appetite, anorexia, and various forms of dyspepsia may *afflict some patients with this disease occasionally or much of the time.*

Others, on the contrary, have a voracious appetite for days, or only occasionally, alternating with lack of appetite. Often, only a short time after a hearty meal the patient feels the need of eating again. But even during the

meal he soon not infrequently loses the desire to eat. Morbid hunger accompanies vomiting and diarrhoea, with a rapidly progressive emaciation. In the case of a 46 year old male patient of Chvostek (400, 23rd observation) an insatiable hunger developed with the beginning of improvement of the malady, after previous emaciation with lack of appetite and severe diarrhoea During this recovery period the body weight increased by 14 kg Exceptionally, this voracity is the first symptom of the disease, as, for example, in Grunfeld's (1445) case of a 33 year old woman who experienced an increase in appetite immediately after intense mental excitement.

Voracious appetites were described by v Basedow His account was followed by the descriptions of Aran (78), Trousseau (219), Baumler (203), Benedikt (348), Boettger (349) J Russell (567) mentions *bulimia* in the case of a 32 year old woman who had diarrhoea, vomiting and a great loss of weight, Renault (931) with enormous emaciation, Dinkler, (1711) in the case of a 42 year old woman during a severe exacerbation of the disease following continual vomiting, Moutard Martin (2326) in the case of a 26 year old female who had diarrhoea A 32 year old female patient described by Mannheim (1222) had typical voracious appetites, especially at night A 32 year old man whose case history Isaak describes, could scarcely wait until meal time But when food was offered he turned away in disgust and could eat nothing

Grohmann (1202) noted *bulimia* once among 14 cases, Passler (1362) 13 times among 51 cases, Kocher (2197) 6 times among about 80 cases, sometimes combined with diarrhoea and vomiting Among Kocher's cases, loss of appetite was found rarely and independent of digestive disorders A few of his cases disliked certain foods, for example meat or milk He also reports a 22 year old woman and a 36 year old woman who had an abhorrence of certain foods

In 20 among 180 of Murray's (2553) cases, disorders of the appetite were mentioned, in 4 cases the appetite was reduced, in 16 it was increased or voracious Among Riedel's 50 patients with Basedow's disease 7 at times had excessive appetites (Schultze 2749) Among my own 95 cases increased appetite or voraciousness was mentioned 23 times, 5 times it alternated with loss of appetite and 7 times it was accompanied by diarrhoea, 6 patients complained of lack of appetite, 19 had normal appetite and in the rest of the cases no information is presented.

It is probable that the increased need for nourishment which occurs not infrequently in patients with this disease is related to an increased metabolism

§172. The most common disorder of the digestive organs is a diarrhoea which takes a very characteristic form. Apparently without any cause, and starting very suddenly without any colic-like pains, there are 4 or 6 watery discharges within a short time. The stools are grayish or bright yellow, and not infrequently look more or less like bile In the latter case the presence of unchanged bile can be demonstrated Sometimes such an attack lasts only a few hours, in other cases the attacks occur in daily succession for several days and stools are passed 10 or 15 times a day. These attacks defy

all the usual therapeutic measures Then they disappear just as suddenly as they came, whereupon the intestinal function returns to normal again But it is not seldom that the diarrhoeas occur again with repeated relapses after shorter or longer intervals. There are cases in which the attacks last weeks or months or even over one year If the diarrhoea attacks do not last too long and are not too profuse the patients can feel fairly well during that period They continue to eat with good appetite and some are voracious If profuse diarrhoea attacks continue longer they become agonizing to the patient and can take on a threatening aspect. The patients lose much weight thereby and death is hastened if persistent vomiting occurs at the same time In severe cases of Basedow's disease diarrhoea is almost never absent at some time in the course of the illness Fr Muller (1134) was struck by a boat-shaped hollow in the abdomen which he attributed to emptying of the intestine In many patients attacks of diarrhoea are brought on by minor psychic stimuli.

Sometimes diarrhoea appears in the developmental stage of the disease

This occurred in the first of the cases described by v Basedow (15), a woman of about 27 years In one of Chvostek's cases (400, 23rd observation), a 46 year old patient, *severe diarrhoea began directly at the start of the illness* This diarrhoea continued until the patient became debilitated Similar reports are given by v Mieulicz (2102), Thomson (1158), Cialinski (2052), Bruns (2268) and others Kocher (2197) mentioned diarrhoea at the beginning of the disease in 4 cases Mobius (1478) reported a female patient who complained of headache, sleeplessness, and, in the final two weeks, of a diarrhoea which ceased just as suddenly as it had begun There was a small goiter and a tachycardia Other symptoms of Basedow's followed In Fr Warner's case (2032) the disturbance began with a diarrhoea of nine months duration In 2 out of 22 cases reported by v Mather (2541) the disease symptoms began with attacks of cardiac palpitation, continuous diarrhoea, and vomiting A 28 year old woman whose case history is presented by Thorbecke (2580), had cardiac palpitation Occasional diarrhoea attacks were the first symptoms They occurred in combination with an influenza Also, in the later course of the disease, which ended in death, a periodic profuse diarrhoea was a prominent symptom Shortly before death the stool became bloody In 3 of 46 cases from the Breslau medical clinic, as collected by Donchin (2644), diarrhoea was present right at the beginning of the illness One of the 3 Basedow's disease cases described by Morse (6865) started with *diarrhoea and tremor*

Occasional watery diarrhea and constipation may alternate Sometimes, after the final cessation of the diarrhoea a period of obstinate constipation occurs as a sign of *atonia* of the intestine. More rarely constipation with intervening episodes of diarrhoea occurs.

Following v Basedow, Stokes (46) mentioned diarrhoea in the symptom pattern of Basedow's disease in the case of a 48 year old man with a concurrent exacerbation of all symptoms, Gros (64) in the case of a 40 year old lady with subsequent obstinate

vomiting attacks, Trousseau (219), Bruck (112) Baumler (203), Morell Mackenzie (214), Cheadle (223), Roesner (340), H Vogt (370), Chvostek (252), Chairman (377), Rey (393), Yeo (396), J Russell (567), H Vogt (370), Ballet (535), Charcot (613), Jaccond (773), Eger (464) together with uncontrollable vomiting (see below), Merklen (494), Gwynne (897), Dinkler (1711) The last four described the acute cases, as did many others Yeo, and later especially Charcot (613 and 816–7) have indicated the importance of these symptoms in Basedow's disease

Murrell (474), Savage (568), P Marie (670), A Maude (988), and Arneill (1934) described cases in which profuse diarrhoea in combination with uncontrollable vomiting hastened death

Concerning the frequency of occurrence of diarrhoea, a collection from reports of various observers of a large number of cases gives some information.

The occurrence of bouts of diarrhoea was noted by Pierre Marie (555) 216 times among 15 cases, S West (686) 7 times among 38 cases, Westedt (871) 2 times among 6 cases, H Mackenzie (918) 8 times among more than 30 cases, Ch E Renault (931) 10 times among 24 cases, A Maude (922) 4 times among 9 cases, Cohen (1031) 6 times among 16 cases, Grohmann (1203) 3 times among 14 cases, Manneheim (1222) 12 times among 47 cases In the case of a 32 year old female who also showed hysterical signs, attacks of diarrhoea lasting the four or five days came when menstruation, which had been absent for several years, would have occurred In the intervals digestion was normal Diarrhoea was noted by Ditisheim (1293) in 3 of his 17 cases, Passler (1362) in 23 among 51, Hunerfouth (1735) in 3 among 18 cases, Reinbach and v Miculicz (2010) observed it 3 times among 18, Kocher (6197) 40 times among 80, Bruns (2268) 11 times among 27 cases and Murray (2253) 53 times among 180 cases Constipation occurred in 16 cases, in 20 there were numerous but normal stools Kroug (2700) noted intestinal crises in ¼ of his 106 cases Donchin (2644) mentioned diarrhoea in 20 out of 46 cases, Frank Billings (2806) in 12 among 61, and Landstrom (2849) in 6 among 52 cases Among my own 95 patients, chiefly ambulatory, diarrhoea occurring in attacks is noted 13 times, 3 times alternating with constipation One patient suffered from constipation habitually

When we count up the frequency of these symptoms, which are, to be sure, taken from not entirely similar material, we find diarrhoea in nearly 30% of the cases of Basedow's disease.

Salomon and Almagia (2972) report fatty diarrhoea in 2 cases of Basedow's Disease In the case of a 23 year old man it was demonstrated by careful metabolism tests together with concurrent tests with pancreatin, that this was not the result of malfunctioning of the pancreas, but a purely resorptive disturbance of the intestine The fat was always thoroughly mixed with the material of the *faeces* and did not form a layer of fat upon the stool The addition of pancreatin produced no change in the condition The same condition was determined also in several other less carefully studied cases of Basedow's disease In the second case, a 27 year old male, signs of a pancreatogenic fatty diarrhoea were established In this case the Basedow's disease was complicated by diabetes The autopsy showed a block of the small pancreatic ducts by concretions.

§173. Vomiting attacks are a less common, but often agonizing and sometimes ominous development. They begin, like the bouts of diarrhoea, without demonstrable cause. The vomitus is usually clear and the episodes without relation to the intake of nourishment. It is watery, sometimes glairy, more rarely bile colored matter is expelled, sometimes only in the morning. Usually and more frequently, however, the attacks occur 10 or 20 times a day. Occasionally, the vomiting occurs only in short paroxysms, in many cases, however, it continues for weeks or months and then stops as suddenly as we have seen it happening with diarrhoea. In many cases appetite is retained in spite of the vomiting, in others a loss of appetite occurs. There are patients who vomit after every meal losing everything they have eaten. In severe cases vomiting continues almost ceaselessly. The patients then become extremely run-down and not a few die of exhaustion. Many recover, however, after the cessation of the vomiting, and after having believed themselves near death from weakness.

Such was 1 case of Gérin Roze (828), a 36 year old woman. From the very beginning of the illness severe gastric symptoms were present but this patient was completely and permanently cured. Hingston Fox (963) reported 1 case in which vomiting and diarrhoea threatened the life of the patient. Hosslin's (1450) 66 year old male patient, during severe attacks of tachycardia, was the victim of uncontrollable vomiting which brought him close to death from exhaustion. A 22 year old woman observed by G. v. Voss (2353) had a sudden relapse of Basedow's disease with more and more frequent and finally continuous vomiting until the patient lay exhausted with half-closed eyes. After an injection of sodium chloride solution improvement began and gradually progressed until the girl once more was able to work.

Other cases with long continued vomiting ended in death. Thus in Baumblatt's (291) 1 case violent vomiting and agonizing attacks of dyspnoea preceded exhaustion and death. A patient of P. Marie died during a phase of uncontrollable vomiting and diarrhoea. One case of Fraenkel (1572) likewise ended fatally after an interval of ceaseless vomiting. In 3 among Murray's (2353) numerous cases vomiting continued up to the point of death from exhaustion.

In cases of Basedow's disease with acute progress, usually ending fatally, uncontrollable vomiting frequently is added to the other severe symptoms.

In the case of a 32 year old woman observed by Eger (464), a violent emotional excitement preceded vomiting which continued with brief pauses, until death occurred the sixth week after the appearance of the first severe disease symptom. During her last five days the patient vomited continuously. An acute fatal case described by Hardy (548) was that of a 45 year old woman, there was vomiting together with the other symptoms. E. Reymond's (1143) similar case was a 45 year old woman, Ditisheim (1293) had one case, a 28 year old man, one each was reported by Bradford (1538) and by Foxwell (1571). In an unusually acute case studied by E. Harvey Sutcliff (1796), that of a 33 year old woman, uncontrollable vomiting began three weeks before death. Even the sight of food caused retching which did not cease until some mucus had been brought up. The patient then refused all nourishment, even rectal administrations, and died of exhaustion. A 42 year old female observed by

Dinkler had an exacerbation of Basedow's disease with periodic vomiting regularly toward nine o'clock following headaches of three hours duration. After vomiting and retching had lasted six hours a three hour rest followed before the headache returned The emesis material contained only mucus and water, never remains of food After about five weeks attacks of vomiting ceased, followed by voracious appetite and by profuse, watery diarrhoea. A few weeks later the patient succumbed to general exhaustion Arneill's (1934) acute case had uncontrollable diarrhoea and vomiting and a rapid loss of strength before death Similar examples are Dillar's (2169) acute case of a 46 year old woman and 1 case each studied by A J Campbell (2158), a 27 year old woman, and by Atkinson (2254), a 55 year old man

Sometimes vomiting appears among the first symptoms of the disease

A v Graefe (63) mentioned that in 4 among his 8 cases observed up to 1857, vomiting of watery matter occurred during the initial stage of the illness and ceased after several months In one of these cases emesis occurred 10 to 20 times daily. Yeo's (396) 36 year old female, at the onset of the disease, suffered from vomiting and diarrhea In Eger's above mentioned case the illness began with vomiting as in a case of Gaill (544), and of a 31 year old female described by Friedrichson (763). In the case of a 52 year old female whose case history is given by Saint Marie (736), almost ceaseless vomiting together with indications of sclerodermia appeared before the development of the other symptoms of Basedow's disease In the case of a Basedow's disease which began during the pregnancy of a 36 year old female, observed by Haperlin (898), profuse vomiting was among the initial symptoms In the case of a 32 year old patient of Fr Muller (1134) the acutely developing Basedow's disease began with headache and continual vomiting A 29 year old female reported by Putnam (1369) had already had obstinate attacks of vomiting at various times in her life During an influenza vomiting recurred, with varying intermissions, to the point of prostration Directly thereafter came the first of the usual signs of Basedow's disease In a case observed by Passler (1362) the first manifestation of the disease began with emesis after every meal over an eight day period Two of Kocher's (2197) cases, that of a 22 year old woman and a 44 year old woman, had attacks of vomiting [illegible]

every meal during the initial stage of the disease After that she vomited more and more each day, and became progressively weaker Even after admission to the hospital vomiting continued and death was expected daily Finally, vomiting ceased spontaneously together with a fuller development of the other Basedow's disease signs Later a truly voracious appetite developed and by virtue of this emaciation and weakness was gradually corrected

A 20 year old servant girl, as described by K Schultze (2749) had attacks of diarrhoea of obscure origin, and violent vomiting for nine months Her weight fell from 68 to 35 kg Soon after these attacks had ceased swelling of the neck was observed, and soon afterward the usual signs of Basedow's disease A 20 year old female whose history Mesowicz (2413) gives, had pain in the stomach region, loss of appetite, and vomiting among the first symptoms of the developing Basedow's disease Vomiting continued until the patient had to be fed by rectum. She soon left the hospital but died a month later from general exhaustion Similar to this patient was a case, unusual in many ways, described by Boinet and Bourdillon (950) Sharp pains in the stomach region accompanied the vomiting

In most of the cases the vomiting in Basedow's disease is not accompanied by nausea. Payne's (562) 25 year old female had constant nausea as a very troublesome symptom.

As an estimate of the frequency of the occurrence of vomiting in Basedow's disease, I add the following statistical reports of various writers:

Hill Griffith	(658) noted vomiting	12 times among	32 cases
S West	(686)	6	38
Cheadle	(880)	2	31
A. Maude	(992)	2	9
Levin	(777)	3	22
Cohen	(1031)	5	16
Manneheim	(1222)	5	47
Grohmann	(1202)	2	14
Ditisheim	(1293)	5	17
Kocher	(2179)	30	80
Mieulicz Reinbach	(2010)	1	18
Murray	(2552)	11	180
Bruns	(2268)	3	24
Kroug	(2700)	2	10
J Roger	(2736)	2	10

Among 10 fatally ending cases cited by Roper (1911) vomiting is mentioned in 2 Among Riedel's 50 Basedow patients, 12 suffered from frequent unexplained vomiting Among the cases of K Schultze (2749), and in 12 out of 61 of Frank Billing's cases (2806) vomiting is noted 9 times Among my own 95 cases vomiting is recorded 9 times, twice right at the beginning of the disease and 3 times together with severe diarrhoea

A summary of these data shows that vomiting occurs in nearly 15% of cases of Basedow's disease

Miesowicz (2413) tested the stomach content of the patient mentioned above and found a neutral reaction and that it contained considerable mucus In the vomited stomach content he could never discover any hydrochloric acid, and experiments with artificial digestion by added hydrochloric acid always gave a negative result Among the 7 other cases of Basedow's disease which he had the opportunity to study later in the Cracow medical clinic, he demonstrated in 4 an absence of hydrochloric acid but demonstrable mucous content both in the fasting state and after an experimental feeding with egg white Miesowicz is of the opinion that this sign could probably be recognized more frequently in patients with Basedow's disease who suffer loss of appetite if the necessary attention were paid to it.

§174. Federn (757) considers that partial atonia of the intestine is an important factor in the pathogenesis and therapy of Basedow's disease He claims to have found it in all cases of this disease He includes here every

condition in which a part of the alimentary canal, especially of the large intestine, is not able to empty completely. Partial intestinal atonia can occur almost without symptoms; but frequently conditions of various sorts, digestive difficulty, headache and backache, sleeplessness, hysterical states, indeed even mental changes develop from it. Federn found in 1 case of partial intestinal atonia an exophthalmia without other signs of Basedow's disease Treatment for the intestine resulted in improvement. Other observers cannot confirm the frequency of partial intestinal atonia in Basedow's disease Thus, among 14 cases from the Gerhardt's clinic, concerning which Grohmann (1202) reports, partial intestinal atonia was always absent

Schwerdt (1652 and 1789) attributes great importance to atonia of the stomach wall in the pathogenesis of Basedow's disease. General enteroptosis was found in the autopsy of such a case by Askanazy (1690). The stomach and transverse colon, in the case of this 35 year old female, were at the level of the navel, and the small intestine lay largely in the pelvic cavity. Also, both kidneys were moveable. Enteroptosis, however, is such a common disturbance in women that one cannot be surprised when encountering it in Basedow's disease.

§175. The occurrence of icterus in the course of Basedow's disease is relatively rare. It is always a symptom of very serious prognostic significance All the writers who have given attention to this manifestation agree on this: Rendu (565), Jaccond (773), Chevalier (882), Letienne Boix, Mourıquand and Bouchut (2953) In such cases death is to be expected soon Sometimes it begins with bile-colored diarrhoea and vomiting Soon afterward the icterus appears Sometimes blood and albumin appear in the urine. The condition deteriorates rapidly. The patients die exhausted and with indications of a severe intoxication. Autopsy shows the liver filled with blood, sometimes permeated by small hemorrhages. The liver appears to be in a state of fatty degeneration, and sometimes the kidney epithelium likewise The spleen is enlarged in many instances. The intestine is filled with a thin fluid and bile-colored masses. The biliary ducts are open. Nothing can be discovered to prevent the passage of bile into the intestine. From the sum of the clinical and anatomical evidence it follows that, as a rule, the icterus occurring in the course of Basedow's disease is not an obstructive icterus, but a form of *icterus gravis* brought about by toxic influences In rare cases an icterus precedes the development of the Basedow's disease, (Grancher 470—a 37 year old man; W. Begbie 109—a 33 year old man). But in such cases the disease may end fatally after recurrence of the icterus (Begbie).

In Eger's (464) case, already mentioned above (see §173 above) the patient became icteric in the last days before his death, six weeks after onset of the acute disease The autopsy revealed a fatty liver and fatty degeneration of the renal tubular epithelium A 20 year old female was observed by Habershon (310) After a two and a half year course of Basedow's disease, death occurred during a sudden attack of fever and jaundice A swelling at the opening of the *ductus choledochus* seemed to have been the cause There were also pleuritis, pericarditis, and endocarditis Gaille (544) reports an icterus which appeared during an exacerbation of the Basedow's disease a week before death The immediate cause of death given was phlegmonous angina In a severe case described by Bodensteiner (2045) an *icterus gravis* preceded the death of a 24 year old woman Fatty degeneration of the liver was found at the autopsy

In 2 among 13 fatal cases of Basedow's disease which Cleveland (2053) assembled at Guy's Hospital, an icterus occurred shortly before death In a case of Chatin and Cade[1] death followed 1 month after the occurrence of icterus A case described by Mouriquand and Bouchat (2953) is interesting in many ways A 44 year old heavy drinker had several attacks of arthritis All the signs of Basedow's disease developed during the last attack The course was mild at first Later, however, icterus became apparent Profuse bile-colored diarrhoea began Three months after the first appearance of the signs of the disease the patient died The liver was slightly cirrhotic and filled with blood, the bile passages open, the intestine filled with bile The kidneys showed signs of a previous and a recent nephritis The authors considered that the icterus had been caused by hypercholia

Neusser (2720), at the Munich Congress for Internal Medicine reported a severe case of Basedow's disease complicated by pernicious anemia Icterus as well as diarrhoea and vomiting preceded death The autopsy showed atrophy of the liver and of the mucous membrane of the stomach and a large spleen In the case of a 23 year old female patient Paul (174) made an examination three years after the beginning of the disease There was an icteric tint of the skin but only insignificant additional evidence of impaired liver function At autopsy the liver appeared normal in size but very firm The cross section was yellow-colored and granulated, the lobes very small and pressed together by much interstitial connective tissue All the bile-ducts outlets were open The patient had a history of syphilis Other cases, some of them fatal, are mentioned by Chvostek (252) Bertoye (748), Burton (752) Westedt (871), Chevalier (882), Boinnet and Bourdillon (930), and Farner (1129) The latter found an atrophic cirrhosis of the liver at autopsy Eder (2650) describes 3 cases in which icterus occurred in the course of a Basedow's disease of several years duration In one case the jaundice was soon cured by a removal of gallstones, the signs of Basedow's disease, however, continued unaltered It was probably only an accidental complication in this case

§176. Concerning melena and hematemesis see §165, and for cases of throat muscle spasms see §115.

§177. Many patients complain of dryness of the mouth or throat An even less frequent accessory symptom in Basedow's disease is excessive salivation

[1] Un cas de goître exophthalmique, Médecine moderne 1901, p 336

Ptyalism was observed by Pulitzer (217) Chvostek (269, 14th observation), Schönfeld (504) in the case of a 24 year old woman associated with profuse mucous secretion, by Charcot (613), Boedecker (808), Jeunet (1740, 1 case), by Kocher (2197) in 6 among his numerous cases, and by Strumpell (2768) in 2 cases, a 24 year old woman and a 50 year old woman In the latter case the mucous secretion amounted to 105 cc in 24 hours

These latter manifestations probably are, like the abnormal secretions of the tear ducts in some cases of Basedow's disease (see §81 above) to be considered signs of a paralysis or stimulus involving the salivary nerves or the bulbar center (in the area of the glossopharyngeal nucleus).

Signs Involving the Respiratory Organs

§178. Disturbance in function of the organs of respiration generally does not play an important role in the symptomatology of Basedow's disease.

§179. The respiratory rate in patients with Basedow's disease is often rapid, a sign to which Charcot and Marie (555) have called attention already. It can be increased to twice normal, or even more, without the patient's feeling any discomfort, not to mention any sensation of shortness of breath. They sometimes complain of shortness or lack of breath only when climbing stairs or after violent bodily exertion In the cases of many patients tachypnoea is the earliest sign of the illness.

A very intelligent female patient of Passler (1362) herself called attention to this change which had occurred since the beginning of the disease She described the condition as an inability to breathe deeply without having a feeling of shortness of breath In an acute case, which Murray (2213) reports, the respiratory rate was 40 per minute, although the pulse rate hardly exceeded 75 beats per minute After the disease had developed fully the respiratory rate reached 36 per minute with a pulse of 150 beats per minute

A considerable rise in the respiratory rate sometimes occurs intermittently and spasmodically, concurrently with increased tachycardia, sometimes with paroxysms of cardiac palpitation, and, in rare cases, with angina *pectoris* (see §5 above).

Sharpe reports 2 cases (2345) in which he observed such respiratory crises. a 29 year old woman and a 65 year old woman The signs of Basedow's disease were pronounced, only exophthalmia was absent in the latter case Spasmodically, there was an enormous rise in the respiratory rate to 60 or 65 per minute Simultaneously the pulse rate in one woman reached 210 beats per minute The condition was agonizing A 32 year old female patient of Da Costaro (2162) had such dyspnoea at times that there was fear of suffocation. No mechanical obstacle to breathing was present. A 23 year old female Basedow's disease patient from Reidel's clinic at Jena (Schultze 2749) occasionally suffered from such shortness of breath that she had to open the

window to get air There was only a slight enlargement of the thyroid gland During the goiter operation it was evident that the trachea was quite intact Heart and lungs were normal and the laryngoscope showed no obstruction With the cure of the other symptoms shortness of breath disappeared.

The accelerated respiration, as well as the attacks of air hunger and dyspnea in Basedow's disease are, with rare exceptions (see §30 above) not dependent upon the goiter as such, nor upon any disorder in the realm of the respiratory organs Such disorders do not cause acceleration of respiration, indeed, it is sometimes retarded and deep. Examination with a laryngoscope and careful physical examination of the lungs does not reveal any changes except, naturally, those arising from complications Furthermore, the attacks of dyspnoea in Basedow's disease *are not*, as a rule, to be regarded as cardiac asthma caused by congestion in the lesser *circulation following a sudden reduction in the force of heart's contraction* and an insufficiency in the reserve of the left ventricle. However, that such cases of cardiac dispnoea sometimes occur cannot be questioned (§44).

As Hofbauer (2295) has demonstrated by graphs of the breathing movements in a series of cases of Basedow's disease, the respiratory disorders show a definite type characterized by a flattening of the breath curve concurrent with lengthening of the inspiration and expiration, irregularity of form and height of the separate elevations, and intervening stretches of uneven short pauses. This type is found not only in patients who complain of difficulty in breathing but also in those who do not mention any such difficulty

Spasmodic respiratory disturbances are characterized by deeper breathing, rapid inspiration and expiration, and pauses A graph drawn by P Marie (555), which registered the breathing movements of a patient with Basedow's disease brings to light very clearly the characteristics already described by Hofbauer There can be no doubt that the respiratory disturbances in Basedow's disease are to be attributed primarily to a toxic action on the respiratory center

Fenyvessy (1961), at the Vienna Pathological Institute, could produce similar respiratory disorders, increasing or depressing the respiration or arresting the breathing of dogs by injections of large (2 cc) doses of thyroid extract

§180. Basedow's disease patients whose respiration is accelerated usually breathe evenly and apparently without effort There is only a slight measurable difference in the circumference of the thorax during inspiration and expiration *Louise Fiske Bryson (811) first pointed out in 1889 that* patients are frequently unable to bring the thoracic framework back to its normal dimensions after deep inspiration. Graeme M. Hammond (899)

tested this sign in all the cases that came to his attention and suggested that it be called the Bryson sign. Other observers who paid attention to this sign often found it of very little value.

Kalish (911) noted 3 5 cm, Pope (928) 3 cm, Bettmann (1406), by forced inspiration and expiration in a 54 year old female, only 2 cm, Hitschmann (1209) in a 36 year old woman only 1 to 1 5 cm, Mannheim (1222) found, in 7 out of 21 cases, less than 4 cm (the median 2 5), in the other 14 he found between 4 and 7 cm (the median 5) Hugg (1327) observed the sign 13 times among 20 cases. Pässler (1362) found, among normal measurements, also rather small ones, at minimum 2 cm, likewise Patrick (1364) Christens (2473) obtained a measurement of the excursion at the height of the disease of 1 5 cm, after significant improvement this became 5 cm I myself found with non-forced breathing among 16 cases in which recordings have been made, 8 with a difference of 0 5 to 1 cm, 4 with a difference of from 2 to 3 cm, and 4 whose normal values were 4 and 5 cm

L. Fiske Bryson, who found in more than half of her 20 cases that the respiratory enlargement of the chest framework, combined with simultaneous increase in the respiratory frequency, was abnormally small, was of the opinion that the prognosis was serious with a reduction below 1.25 cm I cannot confirm this from my own experience. But I do not doubt that frequent, unusually flat respiration influences the gas exchange in the lungs and thereby the heart action adversely.

It will not be erroneous to attribute the Bryson sign to a weakened condition of the respiratory musculature, analogous to other muscle systems (see §125 above) This view gains support from the observations of Askanazy (1690) who never failed to find the muscle disorder (see Pathological Anatomy of Patients with Basedow's Disease, below) discovered by him both in the diaphragm and in the thoracic and abdominal muscle involved in breathing In one case, in fact, the diaphragm was the first to become affected According to the above evidence it is clear that we have before us a *circulus vitiosus*, to break through which must be the task of realistic therapy (sojourn in pure mountain air, etc ; see under Therapy of Patients with Basedow's Disease).

§181. Kocher (2197) mentioned a condition in several of his patients (also among those with no shortness of breath) which he called "air hunger." Such patients feel well only when they are out of doors. They open the windows, whatever the temperature may be.

Concerning irregular (jerky) breathing see §105 above.

Peter (264) described 2 cases, one a 28 year old woman and one a 50 year old woman (the latter without exophthalmia) Each had pains in the region of the anterior and posterior insertions of the diaphragm as well as in the neck in the region of the left phrenic nerve, and back of the breastbone at the position of the third rib He desig-

nated this manifestation as *neuralgie diaphragmique* Attacks of angina pectoris never occurred in the first patient; the other had only minor indications of it.

Bettmann (1406) mentioned the case of a 54 year old female with attacks of palpitation and shortness of breath The thoracic excursions were usually small and there was sensitivity to pressure over the lower part of the sternum and over the ribs

§182. A dry tickling cough, usually spasmodic, is not an unusual finding in patients with Basedow's disease It is a characterized by a lack of abnormal findings in the lungs, larynx and throat, and is not productive. Sometimes a small expectoration results but this has no relation to the intensity of the cough. By far the largest number of cases of such cough cannot be attributed to the goiter, but to an abnormal excitability in the region of the reflex pathway for coughing Minimal stimuli, which physiologically would not produce any cough, do therefore bring on these coughing attacks Often it is not a matter of actual attacks, but of a frequent dry cough In many cases the cough is a very annoying symptom, especially if the attacks occur in bed and disturb sleep In a subacute case of Fr Muller (1134) a 25 year old female had an occasional cough as an especially distressing symptom during the last five months of the illness. She was compelled to sit up all the time, being less troubled by coughing when in this position. In a severe, unusually acute case of Basedow's disease, a 33 year old female described by Harvey Sutcliff (1796), a distressing cough finally developed into paralysis of the larynx and pharynx

Sometimes a nervous cough occurs among the first symptoms of the developing disease

Lannegrace (718) reported 2 such cases An 11 year old girl had the usual signs of Basedow's disease and a dry cough "like the bellowing of a bull" The attacks occurred every five minutes but ceased when she was in bed A 12 year old girl had a protrusion of the eyes, cardiac palpitation, and swelling of the neck, together with a cough "like the neighing of horses", which disappeared during sleep Both of the cases went on to a complete aphonia In the case of the 12 year old girl other unmistakably hysterical symptoms appeared

The occurrence of a dry cough, often very troublesome, is mentioned in many case histories of Basedow's disease, for example White Cooper (31), Herrman (56), Roeser (71), Aran (78), Trousseau (128), Hanfield Jones (156), Andrews (239), Benedikt (348) Duroziez (403), Bristow (648) Charcot, as early as 1862, called attention to a very troublesome nightly cough (*toux convulsive*) in a severe case of Basedow's disease of an 18 year old girl He later called attention to the significance of this cough as a not unusual accessory symptom of Basedow's disease His pupil, P Marie, (555) studied this symptom more exactly and brought to light the characteristic features of this *toux quinteuse*

A nervous tickling cough does, to be sure, occur also in hysteria and to a slight degree also in anemic patients However, its importance as a symptom of Basedow's disease should not be underestimated.

Joffroy (1117) mentions a case in which there had been such a cough, with rise in temperature, for a long time The patient had been considered tuberculous until the nature of the illness proved to be Basedow's disease

Westedt (871) found a dry, troublesome cough in 3 among 6 of his patients Mannheim (1222) mentioned it 5 times among his 47 cases Passler (1362) 10 times among 51 cases I have noted the symptom 7 times among my own 95 cases

Murray (2213) tells of 2 cases (among 120 cases of Basedow's disease) in which large amounts of watery mucus were expectorated. One patient produced about 300 cc of a foamy, clear, thin mucus during one week, apparently an enormous discharge similar to those we have observed from the intestinal canal (see §172 above)

The exceptional occurrence of hemorrhage from the lungs without any abnormal signs in the lungs themselves has already been mentioned (see §166).

§183. In rare cases alterations of voice have been observed in Basedow's disease. It becomes weaker, and the tone poor, or actually almost lost.

In 1862, already, A Cros (115) mentioned this sign once Trousseau (219) remarked on a change in the voice at the beginning of the disease in a severe case Edwards (886) reported that the voice of a 17 year old female became so rough and toneless that she had difficulty in making herself understood In 3 out of 5 severe cases of Basedow's disease which Fr Muller (1134) observed, the voice underwent these changes, twice with a nasal sound and once without In the latter case the voice later became almost toneless Except for incomplete closure of the vocal cords as a result of a bilateral weakness of the adductors, nothing abnormal could be found in the larynx Baldwin (1265) mentioned a change in the voice in a 45 year old female patient with Basedow's disease who had gradually developed symptoms of myxedema A 33 year old female was reported by Grunfeld (1445); during the development of Basedow's disease the voice became almost toneless The patient suffered from attacks of dyspnea and complained of dryness in the mouth Kocher (6197) recognized a disturbance of the voice among his numerous cases 17 times. Koppen's (1051) 23 year old female patient had previously been a good singer. But her voice became a complete monotone during a typical Basedow's disease complicated by kyphoscoliosis ending in death He also observed the same in the case of another such patient who had developed kyphoscoliosis.

§184. In isolated cases of complication of Basedow's disease with nasal difficulties, these latter seemed to act beneficially on a series of signs of that disease Suitable treatment of the nasal condition brought about improvement, and in a few cases even disappearance, of the Basedow's disease signs. We shall return to this subject in speaking of the etiology of the disease.

§185. We shall pass over the occurrence of purely accidental complications involving the lungs, as, for instance the combination with fibrinous

bronchitis mentioned by H. Fritsche (1102). However, the occurrence of tuberculosis in Basedow's disease deserves a brief survey

Greenfield (1445) held that it was frequent in patients with myxedema, but rare in those having Basedow's disease. This seems to me to be correct in spite of several contrary opinions. Despite the great prevalence of tuberculosis in many regions we still find the combination of the two diseases, at least in a severe form, only rarely.

Hoppengartner (905) gives the case history of a 19 year old girl The symptoms of Basedow's disease had developed rapidly together with the signs of a mild pneumonia in the left lower lobe On the twelfth day after her admission, a sudden decline was followed by death on the following morning Autopsy showed peribronchitis and a diffuse infiltration in the left lower lobe. In a case of tuberculosis with Basedow's disease described by A. Maitland Ramsay (1000), death occurred at an early stage Among 10 cases with fatal outcome, reported by Roper (1911) from the Curshmann clinic, tuberculosis was listed twice as the cause of death Among 24 from the Göttingen medical clinic as reported by Runge (2228), 6 were suspected of tuberculosis but a pronounced phthisis could not be discovered in any Among 120 cases under *Murray's (6613) observation 2 suffered from pulmonary phthisis Among all the* others no physical change in the lungs could be found In the Hamburg Sanitorium for Tuberculosis at Edmundsthal, L. Levy (2530) found, among 170 patients, 13 with Basedow's disease and 14 with various Basedow's disease signs Pulmonary disease was in most cases in an advanced stage

Gilbert and Castaigne (1851) reported a case of Basedow's disease in which a tuberculous involvement of the thyroid gland was found, Stumme (2885) reported a case complicated by signs of tetany The parathyroids were enveloped by an extensive tuberculous area (see §113 above)

It cannot be doubted that, when tuberculosis and Basedow's disease combine, the two diseases affect each other adversely due to the disturbance in metabolism and nutrition respectively, characteristic of each The prognosis is *rendered substantially worse*

Abnormalities and Diseases of the Sex Organs

§186. Menstrual disorders are often found in Basedow's disease The previously regular and normal periods not infrequently become more scanty with the beginning of the disease or during its course, longer intervals occur, or menstruation ceases entirely Dysmenorrhoea may appear With *improvement in the general condition these disturbances disappear* again. New cases sometimes show a tendency to menorrhagia

The frequency and importance of menstrual disturbances has been overestimated Trousseau (128) declared that, according to his experience, almost *all women with Basedow's disease have disorders involving men*struation, and that a favorable outcome of the disease cannot be hoped

for until these difficulties are corrected. If one considers here how frequent menstrual disorders are in general, and how frequently a greater or lesser degree of anemia occurs among patients with Basedow's disease the frequent occurrence of such disorders in these patients should not cause surprise

Hill Griffith (658) found only 6 menstrual disorders among 23 female patients from 16 to 44 years of age In the cases of 3 of these complete amenorrhea occurred for several months or years S West (686) noted irregular menstruation in the case of several of his 38 female patients But each case also showed pronounced anemia. G Berry (807) is of the opinion that the menstrual disorders, when they occur in Basedow's disease patients are to be regarded as the result of anemia R Russell (93) among his 48 female patients observed slight menstrual disorders several times in the course of the Basedow's disease But the great majority menstruated regularly. Among 170 female Basedow patients under G R Murray's (2553) observation, irregularity in menstruation occurred in 45, and amenorrhea of various durations in 24 cases With improvement in the other symptoms, menstruation returned again. Mannheim (1222) noted 7 among 36 female patients whose menses ceased, after the beginning of the disease, for a few months or years Among 8 patients between 20 and 40 they were scanty In the cases of 2 others they were profuse In 19 cases the menses were normal or not quite regular Kocher, (2197) has observed disorder of menstruation with the onset of the disease among his many female patients, this disappeared again when it was cured Almost always it consisted of a decrease or amenorrhea Menstruation became heavier with the appearance of the Basedow's disease in 1 case only He held the reappearance of the menses to be a favorable sign. Mobius (1478) was of the opinion that dysmenorrhea and amenorrhea in Basedow's disease patients is scarcely more frequent than in other patients According to Oppenheim (2107) and 2417) amenorrhea belongs among the rare findings in cases of Basedow's disease

In certain cases, especially those with an acute development of the disease, the menses which previously had been regular suddenly ceased without known cause even before pronounced Basedow's disease symptoms had appeared, and in the absence of all signs of anemia or chlorosis.

Concerning excessive menstrual bleeding and metrorrhagia (see §166 above)

§187. In the majority of cases Basedow's disease does not seriously disturb the progress of pregnancy and birth. Many Basedow patients have nursed their babies themselves. However, cases have been known in which Basedow's disease influenced the fetus unfavorably leading to premature birth or abortion. Basedow's disease seems no longer a danger when it begins during the second half of the pregnancy.

We shall have to deal more fully later with the important influence which physiological and pathological processes in the sexual life of women, especially gravidity and puerperium, play in many cases in the origin and course of Basedow's disease.

In a number of patients with this illness the onset began at the time of the menopause (see Etiology of Basedow's Disease)

§188. Considering the wide-spread occurrence of gynecological diseases we are not surprised to find them often among such patients, the majority of whom are female.

In most cases it is a chance complication. Heusinger (38) found at autopsy scarred atrophic ovaries and a fibroid uterus, Windle (534) noted atrophy of the fibrotic ovaries, Bucerius (2154) found a large myoma of the uterus, a dermoid of the left ovary, and a calcification of the right one. Petithan (734), Mannheim (1222), Eisenhut (1301) each observed in 1 case and Theilhaber (1380) in 2 cases gynecological disorders which had been present before the outbreak of Basedow's disease.

W. A. Freund (618) reported in 1885 that none of his cases of Basedow's disease which he regarded as really chronic and which had gynecological examinations within 10 or 12 years failed to develop atrophy secondary to parametritis. It is well known today that this condition occurs in association with Basedow's disease far less commonly than W A. Freund had supposed Nevertheless it is readily apparent, as H. W. Freund (968) has observed, that among the many gynecological disorders accompanying Basedow's disease secondary atrophy of the pelvic organs is found more commonly than any of the others

Kleinwachter (840) described a Basedow's disease patient of 29, para 3, with secondary atrophy of the sex organs involving particularly the mammary glands. The hair and fat over the pubis and labia was scanty The vagina was patulous and its walls thin The cervix was palpable only as an atrophic bean sized remnant The ovaries were reduced in size but there were no adnexal adhesions The menses and libido had been absent for 9 months The atrophy of the breasts was extreme The entire picture was comparable to a senile atrophy of the sex organs. In the case of a female who had Basedow's disease for 4 years the observations (1049) were comparable but more extreme in form There was a loss of scalp and pubic hair, a striking diminution in the size of the breasts, and atrophy of the right ovary, but little demonstrable change in the size of the uterus In the case of a woman of 32, on the other hand, the menses were sparse and irregular during the Basedow's disease although all other positive findings were absent Following recovery the menses again became regular Cheadle (425) had previously reported underdevelopment of the uterus and ovaries and atrophy of the breasts in 2 of 7 cases Bamours (918) also noted, in one case, an atrophy of the uterus.

Kleinwachter's (840) examination of a 23 year old patient and A. Maude's (992) of a 24 year old female disclosed a thin-walled vagina and a small

prolapsed uterus. Theilhaber (1380) often found atrophy of a part or of the whole reproductive apparatus in women with Basedow's disease. With improvement of the general condition the uterus regained its normal form and consistency Seligmann (1654) reported a presenile atrophy of the reproductive organs in a young female patient with Basedow's disease. A 33 year old female whose menstruation had previously been regular had four normal births, and an abortion without known cause; in this case J. A. Hirschl (1976) discovered atrophy of the uterus. Here signs of myxedema were soon added to those of Basedow's disease, and Hirschl was inclined to consider the uterine atrophy as resulting from the myxedema, as reported by Möbius (see §221 below) In the other known cases of atrophy in the reproductive apparatus no signs were present which would support such a view.

Among autopsy findings in Basedow's disease Hetzel (1114) mentioned the case of a 45 year old female who had a small uterus and hard bean-sized ovaries. The same was reported by Mattiesen (1471) in the case of a 14 year old girl Askanazy (1690) found atrophy of the uterus and ovaries in 4 cases In one case the ovary was transformed into a cyst the size of a small apple.

As contrasted with these findings M. Saenger (859) emphasized that he had not been able to determine any atrophic changes in the sex organs in the 3 cases of Basedow's disease; but there were other minor gynecological disorders. Theilhaber (1380) states that changes in the abdominal region were entirely absent in many cases of Basedow's disease Kocher (2197), among his 64 female Basedow's disease patients, had never found any changes in the reproductive organs This agrees also with my own experience with 80 female patients.

§189. A marked regression of the mammae unrelated to any atrophic changes in the genitalia has been observed a few times To the extent that the signs of Basedow's disease may improve, the breasts also can become fuller.

v Basedow (15) mentioned in his first description atrophy of the mammary glands, Koeben (55) reported a similar observation Tapret (483) observed in the case of a Basedow's disease patient a reduction of one breast With progressive improvement of the disease this breast again attained a greater fullness Mooren (523) observed atrophy of both breasts in the case of a 38 year old female Coracussi (813) refers to such a case Among 36 female patients Mannheim (1222) noted regression of the breasts in 2 cases In the case of a 37 year old emaciated female it amounted to complete disappearance of the breast glands accompanied by loss of all the hair on the pubis; in the case of a 28 year old female without general emaciation a rapid atrophy of the mammae was observed Kocher (2197) noted a disappearance of the breast glands in 17 of his 64 patients after the beginning of Basedow's disease; but in no case complete atrophy. Cholmogoroff (1545) observed atrophy of the breast glands

in the case of a 32 year old Basedow's disease patient during her eleventh pregnancy, although she was in the second half of it Six months after a normal birth there were distinct signs of the illness. The uterus was small and the external genitalia atrophied A 26 year old female reported by Moutard-Martin (2326) had atrophy of the breast glands, loss of hair, and the usual Basedow signs

§190. In the male sex a noticeable regression of the testes has been observed quite exceptionally, as by Walzberg (371) in the case of a 20 year old shop assistant, and by Kocher (2197) in the case of an 18 year old farm worker, in addition to the absence of sexual impulse. Since the latter case, in addition to the signs of Basedow's disease showed signs of myxedema it would probably be more correct to connect the atrophy of the testes with the latter Reduction of loss of sexual impulse and the *potentia coeundi* has been recognized several times in men from the onset of Basedow's disease or during its course. It may be that the poor general condition in many of these cases can be held responsible Reinbach and V Mikulicz (2010) report a 46 year old male patient with Basedow's disease whose 4 years of impotence disappeared after almost complete recovery from the disease brought about by a goiter operation.

§191. Still less common than the atrophy of the mammae is an unusual development of the breast glands in Basedow's disease patients in striking contrast to the general emaciation

v Basedow (15) saw this unusual symptom in one of his patients The breast glands of a 50 year old man who suffered from a pyogenic infection of both eyes, became much enlarged The left breast became covered with a bluish red network of veins, with hard nodules and cords The breasts exuded colostrum and were painful v Mikulicz (Rimbach 2010) in the case of a 52 year old man with pronounced Basedow's disease observed an enlargement of the mammary glands on both sides the size of half a lemon They were not painful to the touch and gave no indications of inflammation A week after the ligature of four thyroid arteries the breast gland enlargement diminished Hill Griffith (658) reports a 24 year old female During an episode of Basedow's disease the hair on the head fell out, the mammae became enlarged and remained so

Urticaria attacks in Basedow's disease have been described by Bartholow (326), Bulkley Duncan (330), Roesner (340, 1 case) Rolland (364), Homén (770), Dauscher (820), Leflaine (845), Buschan (1181), Souques and Marinesco (1660) and others

§192. The descriptions just given reveal that the changes occurring in the reproductive organs in many patients with Basedow's disease certainly are not a simple coincidence. We have seen that such changes sometimes develop only with the onset or during the course of Basedow's disease and sometimes disappear at the time of improvement or cure of the latter I do hesitate to consider them in such cases as unusual and rare Basedow's disease signs, analogous to other so-called trophic disturbances.

We shall in another section have to deal with the influence of gynecological ailments upon the occurrence and course of Basedow's disease. We shall also see that, in a number of cases, the correction of gynecological ailments brings about an improvement or cure of the Basedow's disease.

Signs Involving the Skin

§193. We have, in a preceding paragraph, become acquainted with various skin changes in Basedow's disease dependent upon vasomotor disturbances (see §163 ff above). However, more or less rare accessory skin signs also develop, probably characteristic too, which are to be classified as angioneuroses and trophoneuroses.

§194. These include, first of all, *urticaria.* Sometimes its occurrence is quite transitory, the eruptions disappear after less than an hour or after several hours, in other cases it is of longer duration and the itching and disturbance of the nightly rest can cause great misery. It can go away as an eruption, more frequently, however, it returns with a certain regularity during several weeks or months Sometimes the wheals are confined to a small region of the body and can, thereby, change position; other times they extend over the entire surface of the body

In one case of Rosenblatt (5171), after a great fright, transitory urticaria occurred along with tremor of the limbs, and various vasomotor and nervous symptoms, only then did the further signs of Basedow's disease become apparent A 27 year old female whom Balacescu (2145) reports suffered innumerable outbreaks of urticaria in the course of Basedow's disease before the symptom complex of the latter had reached full development In a 22 year old female whose history is given by V Mathes (654), the disease began with urticaria over the entire body for two days, followed by a severe headache The patient became irritable and lachrimose and often had

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In the cases of Wherry (743) and Burton (752) the urticaria appeared every morning and lasted one to two hours P Marie's (555) 51 year old patient exhibited the peculiarity that every time that she went to the country she got an urticaria which

was the case of a 54 year old female described by Bettman (1406) After the complete development of the Basedow's disease symptom complex with various accessory signs urticaria developed following an attack of violent vomiting and diarrhea, which spread over the entire body Six months later, with deterioration of the general condition, the signs of diabetes appeared Elliot's (2488) 54 year old male with Basedow's disease, diabetes, and albuminuria had a transitory attack of urticaria

A 20 year old male, whose case history Joseph (909) describes, had six years of

urticaria irregularly over the whole body and scalp On hands, feet, lips and several times on the tongue appeared circumscribed swellings which did not itch or redden. This was an acute circumscribed Quincke's edema (see §210 below) The single weals were of various sizes, and met to form giant weals, but they remained definitely distinguishable from the swellings of acute skin edema After two years the signs of Basedow's disease were fully developed

Among 17 Basedow cases, which Renault (931) collected from Paris hospitals, a single temporary attack of urticaria was mentioned (in the case of an 18 year old girl) Among 47 cases Mannheim (1222) noted periodic urticaria among 4 women (ages 26, 32, 40 and 51) Among 3 of 24 patients from the Erbstein clinic (Runge 2228) urticaria was observed Kocher (2197) found in 4 of his cases multiple urticarial eruptions over the entire body Two sisters had it often since the beginning of the disease, particularly after great excitement In these cases occasional urticarial attacks also occurred after the Basedow's disease had been cured by surgical interference In the other two cases skin eruptions remained absent after the cure of the disease

§195. *Pruritus* or troublesome skin irritation, especially without the formation of efflorescences and without the action of an outer stimulus, is a very rare, but, in respect to pathogenesis, a not unimportant sign of Basedow's disease. In typical cases of this sort it is not a matter of accidental combination but probably has a closer connection with the other Basedow's disease symptoms With an improvement or cure of the disease pruritus can disappear again. In this regard it should be mentioned here that pruritus also has *accompanied alimentary thyroidism, but only in exceptional cases* (Ewald 1427 and 1427a, H Mackenzie 1881) The pruritus with Basedow's disease is probably analogous to the itching that is encountered sometimes in chronic gastritis, icterus, *diabetes mellitus*, chronic renal disease, or arsenic poisoning It may be attributed to some foreign substance of a toxic nature which acts as a peculiar stimulus on the sensory nerve endings

Naturally, in cases of Basedow's disease patients who complain of itching, one must ascertain whether any of the above complications are involved which could be held responsible for the pruritus In any case it is desirable to look into this matter even in cases where the patient does not complain of itching

Budde (879) reports a 53 year old female who had Basedow's disease for three years Attacks of burning heat over the whole body and itching without sweating occurred These later were accompanied by cardiac palpitations A short time later urticaria broke out followed by diabetes and death (see §194 above)

An itching dermatitis spreading all over the body was described by Lewin (777) in the case of a 28 year old female with Basedow's disease Later, reddened spots appeared and developed into small colorless blisters Hirschl (1208) reports pruritus in a case from the Kraft-Ebbing Clinic, another is given by Popoff (1899) A man with Basedow's disease observed by H Mackenzie (1881) suffered from an unendurable torturing itch when in bed Mackenzie, in this connection, calls attention to the fact that itching of the skin can also be observed in myxedema patients who had been treated with thyroid gland preparations Reinbach (2010) mentions pruritus

in 3 among 18 cases from v Mikulicz's clinic. Following the cure of Basedow's disease by operation the itch disappeared along with most of the other symptoms In one of these cases, however, the skin was described as dry and scaling In another case of Basedow's disease cured by operation described by v. Mikulicz (2102a) at a clinical meeting of the Schleswig Society for Indigenous Culture, ascites, edema of the legs, and severe pruritus occurred James Nevins Hyde (2299) reports two patients with Basedow's disease, 42 and 49 years old, who suffered from pruritus The latter had angioneurotic edema (see §210 below) We are indebted to Bertels in Riga for information on two carefully investigated cases (2460 and 2616) A 38 year old unmarried

of careful internal and dietetic treatment the condition continued to deteriorate until an operation on the left thyroid lobe was performed by A. V. Bergmann The operation produced at first a temporary, then a lasting improvement which was aided by bath treatments Fourteen months after the operation all signs of Basedow's disease had disappeared The itching disappeared completely An influenza attack three years later caused a relapse with pruritus

The second case was a 23 year old woman who had a miscarriage, was depressed, developed cardiac palpitation, a nonpulsating thyroid enlargement and heat sensations About a year after the beginning of these manifestations, pruritus also appeared A year later the Basedow's disease improved with a new pregnancy followed by a

able chiefly on the scalp and the ears Sokolenski (2438) who declared on the basis of his experiences that pruritus is not a rare symptom, even in mild cases of Basedow's disease, considered that the tendency of the itch to become localized, especially around the ears and on the whole scalp, was peculiar to this disease J B Möbius (1886) mentioned that itching of the face was a complaint of two of his Basedow patients They stated that the itch started from the nasal mucous membranes and extended to cheeks and chin One of my patients had an itch on the left side of his face Kroug (2700) noted pruritus only once among his 106 cases of Basedow's disease Since it only rarely reaches a disturbing stage spontaneous statements about it usually are lacking.

With this survey of the known observations it is impressive that only a few of them were made in western Europe and England and only one in North America. One case was published in Scandinavia. The rest emanate entirely from the eastern part of Germany and from Vienna, and the majority from Russia.

§196. For the sake of completeness we add further that Trousseau (219) once observed *herpetiform eruptions* on the skin of a patient with Basedow's disease.

In one of my cases, a 27 year old female teacher, a *herpes zoster occipitalis* of the right side, with much pain, developed in the course of Basedow's dis-

ease. When I examined the patient, I noticed prominent, bright red, keloid-like scars in a circumscribed area near the hairline.

§197. *Erythema nodosum.* Ed. Schiff (2343) described as vasomotor disturbance a peculiar affection of the skin of a woman suffering from Basedow's disease. On several fingers of both hands, and especially about the joints, hard livid red lumps appeared, the size of hazelnuts, and having an appearance like that in erythema nodosum. The skin disease had first appeared 3 years before After that it had appeared and disappeared repeatedly

Much earlier the occurrence of erythema nodosum in Basedow's disease was mentioned by Rieger and V Forster (500) in the case of a woman who had suffered from this disease for 12 years Eckervogt (516) described, in the case of a 22 year old patient, the occurrence of patches of various size, raised slightly above the surface of the skin, reddish blue and irregular in form, spreading from the calves of the legs to the knees, and appearing right at the beginning of the Basedow's disease. The erythema spots appeared first on the right lower leg and then on to the left one

Erythema nodosum must be considered a condition closely related to infectious diseases Its occurrence in Basedow's disease is probably due to a toxic action of this disease upon the blood vessels of the skin.

§198. In closing I would like to mention an interesting observation of Hosslin (4050) His 22 year old patient exhibited certain changes in the mucous membrane of the tongue, known as *leucoplacia buccalis*, that is, circumscribed white spots, which according to Schwimmer[1] developed from red-colored spots (*stadium erythematosum*) v Hosslin considered these the manifestation of a vasomotor disturbance The worse the patient was feeling the more distinctly the *leucoplakia* stood out With the cure of Basedow's disease the mucous membrane patches on the tongue also disappeared

§199. A separate observation is the occurrence of multiple, spotty *telangiectasia of the skin as described by Letienne and Arnal (1605) in the* case of a 27 year old female Basedow's disease patient In the course of the illness increasing numbers of round dot-like flecks developed having a diameter up to ½ cm, with dark red centers and paler periphery formed by fine blood vessels

This dermatosis extended over the whole skin with the exception of face, neck and shoulders The patches increased in size and did not regress with improvement of the general disease

[1] Die idiopathischen Schleimhautplaques der Mundhohle Wien, 1878, and Real-Encyclopädie d ges Heilk , XII, 1887

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A year later the Basedow's disease improved with a new pregnancy followed by a normal birth, and the itching also disappeared These observations of Bertels were presented to the Society of Doctors in Riga Schonfeldt (2435) also mentioned a case of Basedow's disease with pruritus in the case of an elderly lady The itch was noticeable chiefly on the scalp and the ears Sokolenski (2438) who declared on the basis of his experiences that pruritus is not a rare symptom, even in mild cases of Basedow's

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Erythema nodosum *must be considered a condition closely related to infectious diseases* Its occurrence in Basedow's disease is probably due to a toxic *action of this disease upon the blood vessels of the skin*

§198. *In closing I would like to mention an interesting observation of* Hosslin (4050) His 22 year old patient exhibited certain changes in the mucous membrane of the tongue, known as *leucoplacia buccalis,* that is, circumscribed white spots, which according to Schwimmer[1] developed from red-colored spots (*stadium erythematosum*) v. Hosslin considered these the manifestation of a vasomotor disturbance The worse the patient was feeling the more distinctly the *leucoplakia* stood out With the cure of Basedow's disease the mucous membrane patches on the tongue also disappeared

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This dermatosis extended *over the whole skin with the exception of face,* neck and shoulders The patches increased in size and did not regress with improvement *of the general disease.*

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in 3 among 18 cases from v Mikulicz's clinic. Following the cure of Basedow's disease by operation the itch disappeared along with most of the other symptoms In one of these cases, however, the skin was described as dry and scaling In another case of Basedow's disease cured by operation described by v. Mikulicz (2102a) at a clinical meeting of the Schleswig Society for Indigenous Culture, ascites, edema of the legs, and severe pruritus occurred James Nevins Hyde (2299) reports two patients with Basedow's disease, 42 and 49 years old, who suffered from pruritus The latter had angioneurotic edema (see §210 below) We are indebted to Bertels in Riga for information on two carefully investigated cases (2460 and 2616). A 38 year old unmarried woman developed cardiac palpitation, headache, trembling, emaciation and a swelling on her neck directly following a very stormy voyage during which she had been very seasick and in great fear Six weeks later a disturbing pruritus occurred In spite of careful internal and dietetic treatment the condition continued to deteriorate until an operation on the left thyroid lobe was performed by A V. Bergmann The operation produced at first a temporary, then a lasting improvement which was aided by bath treatments Fourteen months after the operation all signs of Basedow's disease had disappeared The itching disappeared completely An influenza attack three years later caused a relapse with pruritus

The second case was a 23 year old woman who had a miscarriage, was depressed, developed cardiac palpitation, a nonpulsating thyroid enlargement and heat sensations About a year after the beginning of these manifestations, pruritus also appeared A year later the Basedow's disease improved with a new pregnancy followed by a normal birth, and the itching also disappeared These observations of Bertels were presented to the Society of Doctors in Riga Schonfeldt (2435) also mentioned a case of Basedow's disease with pruritus in the case of an elderly lady The itch was noticeable chiefly on the scalp and the ears Sokolenski (2438) who declared on the basis of his experiences that pruritus is not a rare symptom, even in mild cases of Basedow's disease, considered that the tendency of the itch to become localized, especially around the ears and on the whole scalp, was peculiar to this disease J B. Mobius (1856) mentioned that itching of the face was a complaint of two of his Basedow patients They stated that the itch started from the nasal mucous membranes and extended to cheeks and chin One of my patients had an itch on the left side of his face Kroug (2700) noted pruritus only once among his 106 cases of Basedow's disease Since it only rarely reaches a disturbing stage spontaneous statements about it usually are lacking.

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§200. Occurrence of *purpuric spots* and exceptional greater bleeding in the skin in Basedow's disease we have already mentioned above (§166).

Pigmentation Disturbances of the Skin

§201. Abnormalities of pigment content in the skin are not infrequently encountered in Basedow's disease, including loss of pigment as well as pig*mentation, and also both changes combined.*

§202. Vitiligo, the occurrence of larger or smaller round or irregularly shaped white spots is sometimes confined to certain regions of the skin. It frequently extends over fairly large areas. Not infrequently it is arranged rather symmetrically In exceptional cases, the discoloration extends over the entire body surface including the hair. In most cases the pigment content of the skin is found to be increased in the neighborhood of the white spots, and this pigmentation usually becomes the more intense, the more the white spots increase. The colorless places thus become even more conspicuous

The appearance of single vitiligo spots was observed by Trousseau (219) in the course of a severe case of Basedow's disease, by Raynaud (338) on the neck of a 25 year old woman, by Drummond (702) in the case of a 36 year old man, Fr Muller (1134) saw it in the case of a 24 year old blond girl on both hands and arms, Jaboulay (1586) in the case of a 57 year old woman, Boinet (1695) in the case of a 48 year old woman with severe Basedow's disease, Faure Jeunet (1740) in the case of a 32 year old woman, Dore (1955) in a typical case which was, to be sure, complicated by syphilis, and Zeitner (2585) in the case of a 27 year old female Delasiauve (229) observed a young girl with Basedow's disease and vitiligo spots on the lower legs distributed as if garter bands had surrounded the legs A Maude (1056) found white spots on brownish eyelids In all the above cases more or less conspicuous pigmentation was present at the same time

B. Ball (278) and Raynaud (338) observed irregular vitiligo spots of various sizes over the whole body of a 24 year old woman In the lumbar region they intermingled to form a complete girdle which stool out distinctly, as did the other spots, against the darkly colored surrounding region Raynaud reports a 25 year old woman who showed white spots which appeared concurrently with the other Basedow signs. A 25 year old girl under Charcot's observation, as reported by P. Marie (670), displayed vitiligo irregularly over the whole body Between these the skin was strongly pigment

signs, and vitiligo spots on the whole lateral portion of the upper leg, following in distribution the branches of the *nervus cruralis*. Two small white spots were also found on the buttocks In the further course white spots appeared on the backs of the hands and the outer sides of the forearms, chiefly along the course of the *n. ulnaris*. In the area of the spots the little hairs were also colorless. In spite of considerable improvement in the Basedow's disease no change in the spots or the pig-

mentation up to the close of the investigation had appeared In the case of a 44 year old female described by Caracoussi (813) white spots on the upper arm and later on the abdomen were observed in the course of Basedow's disease Baginski (1401) observed a 12½ year old girl with Basedow's disease and irregular white spots standing out sharply from the surrounding brownish skin on the head and body With the cure of the disease this disappeared entirely

Low's (1611) 23 year old female patient displayed vitiligo against strongly pigmented skin on the trunk and extremities, especially the waist, elbows, and knees Furthermore there were hard myxedema-like swellings on the lower limbs A similar case was observed by Achard (1933), a woman who had suffered from Basedow's disease for 16 years Three years previously, Faure had cut both cervical trunks of the *sympathicus* In the further course of the disease, vitiligo and loss of hair occurred together with pigmentation of the skin, and a myxedema like swelling of the skin of the limbs and lower part of the abdomen In an acute developing case observed by Fr Kraus (1870) a diffuse pigmentation of the skin with vitiligo spots was a conspicuous sign In the case of a 40 year old woman with severe Basedow's disease observed by Boinet (1695), full development of the symptom complex was associated with a loss of color spreading rapidly over the whole formerly pale brownish skin of the body and a simultaneous blanching of most of the hair on the body With regression of the signs of the disease brown spots appeared on the face It gradually became an intense brown with a few colorless patches Little by little the brown spots spread over neck, shoulders, back and extremities

In Bettmann's (1406) case vitiligo appeared among the first signs of the disease and remained until the end of the observation six years later With the cessation of menses during the forty-eighth year, peculiar white spots appeared on various parts of the body Simultaneously the neck became enlarged and nervousness increased When, later, diabetes also developed, numerous vitiligo spots were found on the dry, brittle, wrinkled skin around the mouth, on the chest, in a zone below the mammae, on the abdomen, in the hip region, and in the region of anus and vulva Everywhere the margin of the spots was formed by a conspicuous dark zone which gradually blended into the normal skin color Neck and backs of the hands were also intensively browned Only on the dorsal sides of the second and third fingers light spots were seen The backs of the feet looked as if they had been sprayed with dark brown spots A Vigouroux (1014) mentioned a case which is worthy of notice In the case of a 27 year old woman vitiligo appeared after great mental excitement and extreme exhaustion and after six years of cardiac palpitation, swelling of the neck, an alteration in the expression of the eyes, and tremor

From the statements of several writers a further idea of the frequency of occurrence of vitiligo in Basedow's disease may be gathered.

Drummond (702), among 24 cases, mentions 3 with vitiligo, once it occurred at the onset in the case of a 27 year old woman Denton Cardew (958) considers vitiligo not unusual in Basedow's disease A Vigouroux (1014), among 14 cases, mentions 3 with vitiligo Mannheim (1222) among his 47 cases, noted 4 with vitiligo The patients were between 32 and 43 years of age In two of them, one a 32 year old woman and one a 37 year old woman, there were such spots together with pigmentation even on the eyelids

§203. Bleaching of the hair in the region of the vitiligo spots has already been mentioned in 2 cases presented (Clay and Boinet) It may well have

occurred without having been noted by the authors. Even without leucopathia a whitening of the hair has been observed in Basedow's disease, sometimes in a single region, sometimes over the whole body.

This whitening of the hair of a female within a short period of time, was seen by Duroziez (301) In the case of a 23 year old woman S West (686) observed that the hair whitened after severe fright, a few months later exophthalmia and cardiac palpitation were followed in a month by swelling of the neck A 36 year old patient of O Kahler (775a) noticed the whitening of certain locks of hair, especially on the left side of the head, one year after the appearance of the first Basedow's disease signs. Westedt (874) tells about fading of the hair in the case of a 33 year old woman Buschau (1181) observed premature whitening of the hair in Basedow's disease In the case of the patient of Boinet (1695) mentioned above, head and body hair, as well as that on the pubis and in the arm pits became entirely white Only the eyebrows remained black In 8 among his cases Kocher (2197) found an early blanching of the hair, usually of all of it, but sometimes only of certain parts In many of his patients the hair became unusually dry and thin Maude tells of a case in which the hair turned white within a few days

Oppenheim (2417) stated that he had found various other changes in hair coloring among his patients with Basedow's disease A 19 year old female patient (2849), during the development of the disease, suffered a loss of hair and of hair color

§204. Abnormal pigmentation of the skin is more frequent than vitiligo in Basedow's disease It can occur in smaller or larger spots, sometimes similar to the *chloasma uterinum* It is more intense in summer than in winter. More frequently the pigmentation appears diffuse and extends over large areas It can vary in intensity of color from a dirty, light-yellow brown through all shades to the darkest bronze. The latter is rather rare, more frequent is the tanning which sometimes appears on parts of the skin much exposed to sunburn The most frequent regions of abnormal pigmentation are eyelids, then skin of the face, neck, region around the nipples, lower part of the abdomen, outer genitalia, arm pits, elbows, and knee joints, in particular the areas which normally have more pigment already. The nipple areas sometimes take on a dark, chocolate brown color. Areas which are constricted by parts of the clothing, garters, etc., are more subject to pigmentation (Carrington 651, Burton 752, A Maude 1056, "garter marks") The darkened spots are in many cases distinctly circumscribed, at other times the abnormal pigmentation blends into the color of the surroundings with blurred outlines Sometimes a striking symmetry of distribution of the pigmented spots is noticeable.

Such was a case of Sainte-Marie's (736), a 31 year old woman with very typical Basedow's disease and conspicuous nervous symptoms. The spots, sometimes separate and sometimes *blending together, were symmetrically distributed over legs and feet* Those on the left were somewhat more intense than those on the right.

The mucous membranes in contrast to Addison's disease are usually unaffected by the pigmentation. Spotty pigmentation has be[en] [ob]served

only exceptionally on the lips, and in the mouth, and on the conjunctival surfaces of the eyelids (Oppenheim 730, Eulenburg 825, Fr. Muller 1134, Kocher 2197, Strumpell 2644; see further statements below).

Very noteworthy and significant for the relationship of abnormal pigmentation to the symptom complex of Basedow's disease is the circumstance that it often regresses and even disappears entirely or except for a few isolated spots with an improvement of the general condition.

This was expressly emphasized in cases of Chvostek (456), Davis (960), Winkler (1086), Hunerfauth (1735), Hirschl (2383) and Rogers (2736)

A spotty pigmentation similar to *chloasma uterinum* was seen by Gueneau de Mussy (492) in 1 of his 4 cases It rose simultaneously with the other symptoms of Basedow's disease Trousseau (219) noticed in one of his cases that the skin, previously transparent, became brown and freckled although it had not been exposed to the influence of sunlight Also, a spotty pigmentation of the skin appeared in a case of a 44 year old woman with a subsiding Basedow's disease and severe diabetes, observed by Morris Manges (2095)

Warburton Begbie (109) in 1862, had called attention to a bronze coloring of the face of his Basedow's disease patients In Germany Friedreich (191) was the first to observe a pronounced bronze coloration of the skin like that of Addison's disease in patients with Basedow's disease This was chiefly noticeable in the face and lasted for a long time after the cure of that illness Soon afterward, Chvostek (224, 6th observation) reported a 30 year old female whose skin was colored a diffuse brownish yellow On the left cheek and toward the outer side of the left eye she had an irregular dark brown spot There were several small diffuse brownish spots on the skin of the lower lip and on the left side of the breast The arm pits and the regions around the nipples were a deep brownish black Eight years later, as Chvostek (456) subsequently reported, the Basedow's disease was completely cured and the abnormal pigmentation had entirely disappeared

An unusually extensive spread of the bronze coloration was found in the skin of Carrington's (651) 23 year old female patient Besides all the above areas of predilection the lower part of the back and the buttocks were strongly colored and countless small dark points were scattered everywhere It was mentioned especially that the girl was of pure English descent and a dark hair color was never known in her family

Drummond (702) reported 6 conspicuous cases of a bronze skin coloration in Basedow's disease In all the cases there was a brown coloration of the eyelids, face, arm pits and regions around the nipples, 4 also showed a brownish pigmentation of the thighs A 36 year old male developed a sharply circumscribed mahogany-brown color of cheeks and neck and a similar discoloration on chest and back The wrists showed white spots with liver-brown surrounding areas In the case of a 28 year old woman the medial aspects of the elbows and the lower abdomen were colored with brown Pigmentation of the mucous membranes was always absent In 3 cases the bronze coloration of the skin was noted among the first signs of the Basedow's disease In the above-mentioned 36 year old patient the appearance of a brown color in the face was noticed as the first pathological sign Heart palpitations occurred only thereafter Gradually the bronze color spread to other parts Soon afterward nervous [illegible] the skin at about the

same time as the palpitation In the case of a 28 year old female patient it appeared simultaneously with a swelling of the thyroid gland preceded by cardiac palpitation and nervousness Three of Drummond's cases ended fatally. In Burton's (752) case, that of a 49 year old woman, the darkening of the skin was noticed soon after the appearance of the other signs of Basedow's disease The dirty gray-brown color was most evident in the face, on the neck and back, in the groins, in the arm pits, under a ring on the finger, and under the knee where the garters pressed With an improve-

In a severe case of Base-

·penheim (730) it consisted

e face, trunk, extremities,

and genitalia The areas around the nipples, *glans penis*, and scrotum were dark-brown to deep black On the upper lip as well as the conjunctiva of the lower lid bluish black flecks were noticed The mucous membranes of cheeks, throat, and larynx were free from pigmentation At that time Oppenheim interpreted the case as a combination of Basedow's and Addison's disease, but later (2107) emphasized expressly that he believed that, from later observation, he had to hold to the assumption of an uncomplicated Basedow's disease even with such extreme pigmentation and involvement of mucous membranes

Eulenburg (825), in a similar case, assumed a combination of Basedow's disease with Addison-like bronze coloration The case was that of a 26 year old Swiss woman, afflicted with severe Basedow's disease in the course of which a mulatto-like discoloration of the skin of the face and hands and a dark brown coloring of the nipples developed The mucous membrane of the mouth also was covered with dark spots In 2 acute cases of Basedow's disease which Fr Müller (1134) observed, the occurrence of a brown coloration of the face and especially of the eyelids was conspicuous even during the initial period of the disease In one of these cases, a 48 year old woman, even the membranes of the gums were marked by several brown spots And in a subacute case of a 25 year old woman, there appeared in the course of the disease an abnormal pigmentation of the face, the *linea alba*, the hands, and, later on, still other parts of the skin The mucous membranes of the mouth also were partially pigmented

Hirschlaff (1733) reports an acute case of Basedow's disease, a 21 year old woman with browning of the face and the whole upper part of the body as one of the first signs of the disease, together with palpitation, general weakness and headache. The mulatto-like discoloration was greatest in the genital region and the arm pits On the chest and neck whitish, pigment-free spots were visible, ranging in size from a knitting-needle head to a lentil The medial aspects in this case were less pigmented than the lateral aspects With a temporary improvement in the general condition and considerable increase in weight the browning diminished, although it was still distinctly evident on the corpse

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the

which Breuer (1944) described a number of cases (see under Etiology below) abnormal pigmentation of the skin occurs as a rare symptom In 2 of such cases, a 32 year old woman and a 37 year old woman, Breuer found a dark pigmentation of the face and neck beside other Basedow's disease signs In the case of a 39 year old female with Basedow's disease Vorster (1257) observed dark gray coloration of the skin of face, hands, and feet. G. R Murray (2213) saw in 1 case general pigmentation of face, neck, lower arms and hands Dark freckle-like spots appeared on the backs of fore-

arms and *hands* In 1 case among 8 Kocher (2197) found a general browning and mucous membrane pigmentation in places

A case of extensive pigmentation was observed by L v Schrotter (2344), a 27 year old woman *previously in good health* *This began in the face, extending up into the scalp and consisted* of light and dark brown irregularly shaped spots, sometimes sharply defined, sometimes blurred, partly arranged in a rather *symmetrical order.* On the back and on the left lower extremity the pigmentation occupied almost the entire region On the edge small circumscribed completely pigment free white spots were visible Also, both upper and lower arms were almost completely brown on the dorsal side and no part of the body was entirely free from this color

J A Hirschl (2383) presented the case of a 36 year old man whose disease had begun three months before with tremor, heavy perspiration, diarrhea, and rapidly progressing emaciation Together with the typical Basedow's disease signs the skin showed extensive bronze coloration which faded out again with the regression of the other symptoms

A 36 year old female observed by the same doctor (2675) had extensive pigmen*tation of the skin, chiefly in the form of freckle-like spots of dark brown color,* which in many places fused with one another The waist and region around the nipples was dark brown

Moutard-Martin and Malloizel (2326) reported the peculiar case of a 26 year old woman Soon after a second abortion, a fine, pimple like exanthema developed from the face and extended over the whole body, fading slowly, without desquamation Following this came weakness of the lower extremities, *tinnitus aurium*, and headache At the same time the patient's attention was called to a darkening of the skin while she herself discovered a swelling on the front of the neck *To this were added, in the course of time, the numerous secondary signs of Basedow's disease* Among the cases assembled by Landstrum (2849) from Sweden, there were 2 with extensive brown coloration of the skin In the case of a 19 year old girl the larger part of the body, including the lower extremities, had a conspicuous bronze coloration In the case of a 59 *year old man* the skin of the whole body became brown with scattered lighter spots on the arms General bronze coloration of the skin was mentioned by Demargne (2481) in the case of a 35 year old female with typical, rather severe Basedow's disease Jeanselme (1213) observed an extensive pigmentation of the skin in the case of a 58 year old Basedow patient with sclerodermia *(see §217 below)*.

§205. In many cases the abnormal pigmentation is confined to face or eyelids S Jellinek (2388) and soon afterward Theillais (2586) described, as a new Basedow's disease sign which seldom is absent, a brownish diffuse pigmentation of the skin of the eyelids which is definitely limited, above by the eyebrows and below by the *margo infraorbitalis* This observation is, however, by no means new, for a pigmentation confined to the eyelids, or *more extensive, has often been described* *It is decidedly less frequent than* Jellinek assumes But a suggestion of browning, in the form of dark shadows around the eyes, without other special signs of pigmentation of the skin is often found among patients with Basedow's disease. A brownish discoloration of the eyelids often occurs as one of the signs of Basedow's disease and frequently extensive pigmentation begins on the eyelids

The brown color of the eyelids can decrease with improvement of the illness or entirely disappear.

Bristow (648) observed strong pigmentation of the eyelids and a dirty-brown coloration of the face in the case of a female of 40 with Basedow's disease Timolheeff, (1159) referring to a 49 year old female patient from Mendel's polyclinic, mentioned dark pigmentation around the eyes In the cases of 2 patients from the same polyclinic reported by Mannheim (1222) the eyelids were noted in particular and a general browning of the face was present Kocher (2197) observed 3 cases with an even pigmentation confined to the eyelids and 5 with pigmentation of the face and particularly the eyelids In several of G R Murray's (213 and 2553) the pigmentation was the most conspicuous on the eyelids and around the eyes or under the lower border of the orbit He designated pigmentation of the eyelids as a common sign In the case of a 27 year old female with pronounced Basedow's disease, Zeitner (2598) observed pigmentation of the skin on the upper and lower eyelids, Stumme (2888) observed it in the case of a 26 year old female A browning of the skin of the lids has also been mentioned by DeMets (2638) and Bryant (2625), each in 1 case of typical Basedow's disease In the case of an 18 year old girl observed by Robinson (2733) pigmentation of the lids was among the first signs of Basedow's disease Later, large spots like

pronounced Basedow's disease cases These included females of 20, 27, 46, and 47, and a 59 year old male with general pigmentation of the skin I myself saw, among 95 cases, only 5 female patients with a slight, diffuse browning of the eyelids. Following the publications of Jellinek and Theillais, I paid special attention to this sign

§206. Concerning the frequency of abnormal skin pigmentation in Basedow's disease, the statements of writers reporting large series of observations are quite varied

While S West (686) found among 38 cases of severe Basedow's disease 1 with pale bronze coloration around the nipples and lower abdomen, H Mackenzie (918) found a more or less pronounced pigmentation of the skin 42 times among 180 cases Drummond (702) declared that abnormal pigmentation of the skin is a frequent occurrence in Basedow's disease Denton Cardew (958) estimated its occurrence at about 70% of the cases Hale White (2250) and Rolleston (2226) considered it not rare John Rogers (2736) saw among 10 cases one with deep pigmentation, a 26 year old female with a severe form of Basedow's disease With improvement the pigmentation disappeared

According to Fr Muller's (1134) experience abnormal pigmentation in Basedow's disease is frequent Among his 5 carefully described severe cases it was evident in 4. Elsewhere also he has repeatedly found pigmentation anomalies A woman with severe Basedow's disease had an extensive brown coloration of the skin. The face and hands were so darkly pigmented that she was taunted by children on the street When the other symptoms improved, the abnormal pigmentation disappeared except for traces. In the cases of 2 women who for years had had large goiters, the signs of Basedow's disease appeared at the same time as an abnormal brown coloration which in one case spread over the whole body and in the other occurred as a dark spotted pigmentation of the face similar to *chloasma uterinum*.

Lewin (777) could report only one instance of abnormal pigmentation among 22 carefully studied cases. Among 47 polyclinic cases assembled by Mannheim (1222) a real bronze coloration was never encountered, but there was an abnormal skin pigmentation among 11 female patients Browning of face and hands was conspicuous in 5 cases although the patients had not been exposed to sunlight In one case the pigment spots were on the forehead and at the borderline of the hair, in another on both cheeks and to a considerable extent on the forehead, in 2 others on the back and chest and in yet another on the elbows and knees Pässler (1362) also never encountered conspicuous bronze coloration among his 51 polyclinic cases, but often found abnormal pigmentation of the skin, usually diffuse and sometimes spotty Among 18 cases from the Munich Clinic as reported by Hunerfouth (1735) one showed a typical bronze coloration of the skin over joints and spine It increased in the course of the disease and diminished again with improvement Among 10 severe cases from the Leipsic Medical Clinic as assembled by Roper (1911) a 37 year old female showed a strong pigmentation of the skin Kocher (2197) saw a general brown coloration 8 times and a pigmentation confined to eyelids 3 times Bruns (2268) observed browning of the skin of the face 3 times among 24 cases Among 22 cases of Basedow's disease from the medical clinic of Halle (V Mathes 2541) a 53 year old female showed numerous pale brown spots on chest and abdomen Among 46 cases from the Breslau Medical Clinic as reported by Donchin (2644) 5 had a diffuse brown coloration of the skin In the case of a 30 year old female this extended to the lining of the mouth In 4 cases the pigmentation was spotty or in fine dots confined to isolated areas of the body Among Landström's (2849) 52 cases of typical Basedow's disease observed in the Seraphimer Lazarett in Stockholm, 2 cases of general pigmentation are noted, and in 4 cases a brown coloration of the face, especially of the eyelids, was present. R Stern found brown pigmentation of the upper and lower eyelids, neck and scrotum More rarely pigmentation occurred around the nipples, the abdomen, and on the *linea alba* in the form of small freckle-like dots In 3 cases the skin was a diffuse brown like that of a mulatto. I myself saw a diffuse browning of the face in only 2 of my 95 cases and in 5, as mentioned above (§205) a pigmentation confined to the eyelids

From the above data it appears that abnormal pigmentation is evident in about 18% of cases of Basedow's disease.

Loss of Hair

§207. A thinning of the scalp and loss of hair is not unusual among cases of Basedow's disease Circumscribed bald spots of *alopecia areata* occur These may become enlarged, fuse with the adjoining ones, and eventually result in baldness

Sometimes the loss of hair extends to other parts of the body, the beard, the arm pits and the pubic region, in rare cases, to eyebrows and eyelashes also Loss of hair from the brows and lashes remains confined to these parts or begins here and in the beard before spreading to the scalp In exceptional cases the loss of hair is unilateral or affects first only one side and later the corresponding areas on the other side With improvement in the general condition loss of hair usually ceases, sometimes new hair begins to grow

on the bald spots, and can actually lead to abundant growth. Sometimes periods of growth and falling hair alternate In many cases, however, the disease may be cured but the hair does not reappear

Kocher (2197) noted an exacerbation of Basedow's disease during which hair and nails grew very rapidly, during a remission the hair fell out freely Two male patients stated that after the outbreak of the disease their beards and body hair grew more rapidly, while the hair of the head fell out

Loss of hair in the course of Basedow's disease is mentioned by Friedrichson (763) in the case of a 31 year old female, Buschan (1181), Dinkler (1953) in the severe case of a 42 year old female, Low (1611) reports a 24 year old female with edema of the lower extremities, Archard (1933) a similar case, Runge (2228) a 44 year old female with browning of the skin, and a 38 year old male, Krieger (2305) a 46 year old female, Jacquet and Gaumerais (2194) and Moutard Martin (2326), 1 case each; K Schultze (2749) 9 among 50 Basedow patients from the Riedel clinic

McHardy (919) found *alopecia areata* in 3 cases of Basedow's disease, once in association with marked browning of the skin

Loss of hair from
(230) in the case of a
and eyebrows, likewis

2 years She was almost bald when she came to Barnes (805) The hair of the head had

out except the eyebrows and an oval place on the skull

Renault (931) reported a 31 year old male from the saltpeter works Four years previously and again simultaneously with the appearance of the first Basedow's disease symptoms, he lost almost all of the hair of the head First the beard, then the eyebrows and lashes, then, two and a half years later, the hair of the head began to go *Alopecia areata* gradually progressed to complete baldness Also, a large part of the

symptom complex, vitiligo, and baldness A. Vigouroux (1010) mentioned a 34 year old male with what seemed to be an incompletely developed symptom complex of Basedow's disease, loss of the hair of the head, beard, axillae and pubis In spite of very considerable improvement in the disease the hair did not grow again Berliner reports (1404) 2 cases of total alopecia in Basedow's disease After a severe shock and drenching during an outbreak of fire, this 30 year old male became weak and dizzy, he complained of palpitation, fatigue and excitability A few weeks later round, bald spots began to appear on the back of the head, and progressed in six months so as to involve the whole body The patient was in a miserable state for about two years After "frightful sweating" had broken out during several nights the general condition gradually improved, but the hair did not grow back. The second case, a previously healthy male of 26, was under treatment by Jul. Kohn for palpitation, dyspnea, sensations of heat, sweating, and *alopecia areata*. In nine months all the hair of the body dropped out, and Basedow's disease was fully developed Also, the nails were

ridged. Berliner also mentions a case of Unna which belongs here A 21 year old servant girl, after having been criminally attacked, developed a right sided hemicrania, epileptic attacks, and signs of Basedow's disease At the same time she lost her hair completely except in the pubic region. The patient withdrew from further study

A 54 year old patient already mentioned several times (Bettmann 1406) lost hair even during the initial phase of the disease Hair was scanty on the head; it was completely absent on *mons veneris* and axillae Boinet (1695) observed a 48 year old female with severe Basedow's disease, complicated by vitiligo spots, and loss of hair from the head and eyelids Jeunet (1740) reported loss of hair from the head, axillae, pubic region, and eyebrows, in the case of a 30 year old female François (2174) discovered loss of hair from the head, and complete lack of hair on the other parts of the body in the case of a female Basedow's disease patient. Disappearance of hair from

Basedow's disease. Later eyebrows and lashes began to fall away

One case of a female who lost hair only from eyebrows and lashes is described by Greenhow (383) Yeo's (396) case, interesting in many ways, was a 35 year old woman who began to lose hair from eyebrows, lower lids, and the medial two-thirds of the upper lid of the left side soon after the left eye began to protrude When the right eye began to protrude six weeks later, the eyebrows and lashes on that side fell out, likewise the hair from the right axilla Wilbrand and Saenger (2033) mentioned the case of a young girl who in the course of Basedow's disease lost eyebrows and lashes of both sides In 6 of Kocher's (2197) cases the eyebrows participated in the loss of hair, and in 1 of Murray's (2213) 120 cases the loss of hair also occurred from the eyebrows and lashes

Loss of hair confined to the pubis, together with atrophy of the genitals, is illustrated in the case of Kleinwachter (840) In another case of the same observer the hair of the scalp was lost also (see §188 below)

In several cases with signs of myxedema added to those of Basedow's disease (see §221 below), loss of hair was also observed, as by Kowaleski (842) in the case of a 46 year old woman with alopecia of the scalp and axillae Ulrich (2028) reported a 19 year old and a 45 year old female whose loss of hair could probably be attributed to the myxedema Fr Peterson (2562) noted *alopecia areata* in the case of a 15 year old girl with Basedow's disease and sclerodermic areas on the trunk

Concerning the relative frequency of the loss of hair in Basedow's disease we gather data from several writers.

H Mackenzie (918) states that most of his patients complained of great loss of hair, but he had never seen complete baldness (2537) Denton Cardew (958) was of the opinion that *alopecia areata* is not rarely found in Basedow's disease In Kocher's (2197) experience loss of hair in Basedow's disease is an uncommonly frequent manifestation In half of his cases more or less loss of hair was noted

Lewin (777) mentioned loss of hair in 1 among his 22 carefully studied cases, Caracoussi (813) in 2 among 6 cases, Cohen (1031) in 3 among 16 Among Mannheim's (1222) 47 cases there were 19, all women, in whom a more or less extreme loss of hair is noted In 3 cases the loss of hair affected the right half of the head especially, in 2 of these the pubic region was also involved, and in 2 others the loss of hair extended also to the axillae and genitals In the case of a 43 year old female periods of new

growth followed losses of hair In 3 among 14 of the cases assembled by Grohmann (1202) loss of hair was evident In 2 among 51 polyclinic patients Passler (1362) noted a loss of hair, in 12 other cases the patients stated that, in the course of the disease, hair fell out Later it usually grew back again

Among 10 fatal cases from the Leipsic Medical Clinic reported by Roper (1911) loss of hair occurred in 3. Among 24 cases from the Gottingen Medical Clinic (Runger 2228) 2 had a loss of hair Renault (931) reported loss of hair in 2 among 24 cases and A Vigouroux (1014) in 1 among 14 G Murray (2553) noticed loss of hair 20 times

case Usually

came entirely

[illegible]

Among my own 95 cases I find hair loss noted 9 times Several times it is mentioned especially at the beginning of the disease, and a new growth followed later

From a summation of these data it is evident that the frequency of hair loss in Basedow's disease is about 23%.

Walsh (2892) has called attention to a hand-shaped alopecia on the forehead, which is often encountered as a congenital disorder accompanying Basedow's disease In 18 cases under his observation it was present every time This band-shaped strip, 1½ to 2½ cm wide at the anterior hairline, may be quite bald, but usually it is covered with small hairs It is not always noticeable at once if the hair on the forehead has been combed toward the front In other cases Walsh has found this alopecia in the form of a band on the forehead in children, as well as in adults, in association with enlarged thyroid glands, tachycardia, nervousness, skin pigmentation, and sometimes tremor

Alterations in Nails and Teeth

§208. Peculiar trophic disturbances are, in rare cases, also encountered in other structures of epithelial origin such as the nails and the teeth.

In the case of J Kohn's 26 year old Basedow's disease patient with total alopecia (see above) all of the nails were flat and cracked Uphoff (2131) reports a 6½ year old girl with Basedow's disease who had very thin longitudinally split nails on both thumbs Among Kocher's (2197) patients the nails of 4 became torn and brittle In one of these cases a general brown coloration of the skin was evident We have already spoken above (§207) about the patients whose hair and nails grew faster during an exacerbation of the disease, 4 of Riedel's 50 Basedow patients (K Schultze 2749) had brittle nails A 22 year old female stated that each time she washed they literally splintered off In the case of Landstrom's (2849) 19 year old patient the nails of all fingers became loosened from the tips halfway to the roots R Stern (2991), in 2 among his numerous cases, found the nails grooved and brittle

The loss of several or many teeth in the course of Basedow's disease has been observed several times.

A woman studied by Koeppen (1051) had kyphoscoliosis (see §219 below) with Basedow's disease and lost most of her teeth Most of the back teeth were missing Two upper incisors and 1 canine were well preserved. Only the roots remained of the others In a case described by Jeanselme (1213) a woman of about 50 with Basedow's

disease complicated by a sclerodermic alteration of the skin (see §217 below) all of the teeth of the upper jaw fell out during the initial stage of the disease within a few months Kowaleski's (842) 46 year old woman with signs of myxedema added to those of Basedow's disease lost eight teeth within two months without apparent cause, a not entirely unusual occurrence in myxedema

The development of dental caries has been rapid in a few cases of Basedow's disease.

Buschan (1181) reports such a case, Mannheim (1222) reports a 21 year old female, Kocher (2197) noted brittleness of the teeth during the course of Basedow's disease in the case of a 23 year old female who had numerous other secondary symptoms also.

§209. Multiple neurofibromes appeared under the skin of the extremities in the case of a 55 year old female According to her statement, these were simultaneous with the appearance of the Basedow signs. They were said to have developed five years before the first visit to my clinic, and were attributed to the effects of a nearby lightening stroke After removal of the neurofibromas in the surgical polyclinic the patient displayed numerous small, linear scars, partly deeply imbedded in the extremities This patient showed unmistakable signs of a complicating hysteria

I have made another isolated observation in the case of a 19 year old girl with typical Basedow's disease under clinical observation About a year after the onset of the disease several small fibromas developed in the subcutaneous tissue of both limbs One reached about the size of a pea They were on both sides of the *sulcus nervi ulnaris*, scattered smaller ones appeared on the dorsal sides of the third and fourth fingers of both hands They were easily movable and not sensitive to pressure Pain resulted only when the lump at the elbow was pressed hard against the ulnaris The fibroma over the left *sulcus nervi ulnaris* and the one on the dorsal side of the right third finger was removed for microscopic examination The others disappeared again after several weeks About two years later a hard tumor developed under the skin over the left *ligamentum patellae* It was the size of a chestnut, movable, and seemingly attached to the patellar ligament The tumor was not painful during palpation but it inconvenienced the patient when kneeling. Sometimes it caused a stabbing pain extending upwards. This swelling also gradually disappeared by itself

Microscopic examination showed that, in this case, it was not a neurofibroma but a plain fibroma The cutis lying over it was normal The tumor consisted of a fibrous connective tissue with fairly numerous cells and the bundles of fibres interweaving in every direction In the middle, the mass was thicker and the bundles wider Toward [illegible]
of the mass contained fairly numerous, thin walled blood vessels with large endothe-

hal nuclei protruding into the *lumen* Elastic fibres which were numerous in the *corium* and in the loose connective tissue surrounding the mass were scanty in the inner portion The tumor from the finger contained a rather large number of polymorphonuclear leucocytes in the intercellular spaces of the connective tissue On Weigert-stained slides it was apparent that no medullated nerve fibres entered the growth, although in the surrounding region some small nerve bundles, cut by chance in making the sections, were plainly evident

Localized Skin Edema

§210. Circumscribed edema of the skin, described by some as acute angioneurotic edema, closely related to urticaria, is sometimes seen in Basedow's disease Fairly large swellings, circumscribed but not sharply marked off, 3–10 cm in diameter, sometimes also larger are typical. They feel hard and elastic to the touch and do not pit after finger pressure The skin surface retains its normal appearance or looks somewhat pale. This edema causes no itching but sometimes makes itself felt by a sense of unpleasant tightness Occurring sporadically, it usually reaches its peak in one to three hours and lasts two or three days or longer In exceptional cases it may appear among the early symptoms of Basedow's disease Most frequently it affects the skin of the face, especially the eyelids and that of the extremities in the region of the joints or over the whole limb. Sometimes only the eyelids are the seat of this peculiar edema. The above described characteristics, especially its localization without relation to gravitation as well as its occasional combination with other vasomotor disturbances distinguish angioneurotic edema from edema caused by the heart disease which, as we have seen, sometimes occurs in Basedow patients (§11). They also distinguish it from the discrasia edema (Millard 780) which, in certain severe cases, follows high grade anemia and is usually localized in the feet and ankles The congestive edemas, quite enormous in isolated cases, occur following cardiac dilatation and relative insufficiency of the tricuspidalis (Přibram 1368, Baumler 1812 and others) and these are not distinguishable from those which are otherwise observed in valve failure *and myocarditis.*

painless swellings at intervals on various parts of the body, especially on the back. They were round. Their diameter was the size of a child's head with the consistency of dough, and covered with normal skin After twelve to twenty-four hours they disappeared again. Quite independent of these circumscribed, acute edemas, there arose later, during an especially severe exacerbation of the disease, a congestive edema resulting from engorgement of the dilated heart, hydropic signs and albumenuria.

An interesting case, which belongs here, is described by M Joseph (909). Fully

five years after the appearance of the unmistakable signs of Basedow's disease a 20 year old male patient had an irregular extensive urticaria over the whole body (see §194 above), while an acute circumscribed skin edema arose on hands, feet, lips, and sometimes also on the tongue No itching occurred in the region of the edema. There was only a feeling of tension During this time urticarial weals and circumscribed skin edema appeared day after day and then remained entirely absent for months A definite cause for their occurrence could never be found A Mailland Ramsay (1000) observed in 1 case transitory, circumscribed edema on the left hand of four days duration, followed by an edema-like swelling of the right hand which likewise disappeared after four days. Homén's (1043) case, age 39, showed a sporadic swelling, lasting sometimes only a few hours, on the skin, hands, legs, and feet and face, especially the left cheek, combined with a feeling of heaviness and tension A Maude (992 and in later publications) had occasion several times to observe among Basedow's disease patients a transitory edema, sometimes unilateral, involving especially eyelids, cheeks, neck, arms and hands

A 30 year old female from Peter's (414) clinic had an edema of the face and extremities, palpitation, slight dyspnoea, headache, and hyperidrosis. The goiter which had been present previously could no longer be felt and the exophthalmia was absent

Evans, (1303) reported a woman of about 30 who, in the third month of pregnancy, began to notice shortness of breath, in the fourth month she noticed a swelling at the front of the throat and a tachycardia The hands and feet were usually moist and felt sticky to the touch Exophthalmia and tremor were absent Hands and feet were swollen The face also had swollen so that it was almost unrecognizable After delivery, violent bleeding and collapse followed Then the Basedow's disease signs gradually disappeared as did the edema Only the goiter remained unchanged Similar difficulties had arisen in previous pregnancies

A 32 year old female with severe Basedow's disease had edema confined to the left side It extended from the back of the foot and the Achilles tendon up to the middle of the lower leg This was the only case of angioneurotic edema among 47 of Mannheim's cases (1222) collected from Mendel's polyclinic The patient also had vitiligo spots, urticaria of the abdomen, loss of hair, and other secondary signs

Pässler (1362) encountered an angioneurotic edema only once among 51 polyclinic cases A 32 year old female showed an edema of the skin on both sides over the lower third of the tibia Of 4 other cases in which a slight edema was observed, 2 showed signs of cardiac disease. In one case mitral insufficiency was recognized, in another case, that of a young girl, edema was attributed to severe anemia

Among the numerous cases of Basedow's disease which H Mackenzie (1614) has described 7 showed an inconspicuous swelling on the eyelids, sometimes accompanied by swellings of the lower extremities, 3 showed edema, either extensive or localized, on the lower limbs J Nevins Hyde (2299) observed an angioneurotic edema accompanied by pruritus in the case of a 49 year old patient with Basedow's disease

Kocher (2197) noted edema in about 25% of his cases Usually it was slight, frequently confined to the ankle region and lower leg, 9 times there was an edema of the face, frequently of the eyelids Whether it was always typical Quincke's circumscribed dermal edema cannot be determined from the descriptions A 42-year old woman had small firm non-sensitive infiltrations in the subcutaneous tissue, especially on the lower surfaces of the extremities These developed sporadically during exacerbations of the other symptoms and disappeared again after a few days or weeks

Acute generalized edema spreading over the lower half of the body was described by Millard (780) in 2 cases

A 58 year old man with plainly developed Basedow's disease signs but no exophthalmia developed a feeling of heaviness in the legs and cramp-like pains in the lower parts ten days after admission to the hospital, when the condition had already improved and tremor was entirely gone At this time edema developed on the backs of the feet and after three days spread over the hips. Three weeks later it disappeared quickly following rather profuse diarrhea A 26 year old woman with an exacerbation of Basedow's disease at the time of a sojourn at the seashore developed an edema of the legs, within 24 hours this had extended above the hips. The face also became edematous The edema diminished while she was lying down and increased again toward evening After six weeks it had completely disappeared. In both cases the heart remained entirely without any organic disturbance

§211. Transitory edema and firm swelling of the eyelids have often been observed in Basedow's disease. These signs affect chiefly the region between the eyebrows and the upper tarsal border. Still more frequent are the edematous swellings of the lids, so slight in degree that small "pockets" are seen between the orbital and lid borders.

Lid edema occasionally occurs as one of the first signs of the disease, as the following have observed· Booth (1408), H. Mackenzie (1614), Sydney Stephenson (2440), Oppenheim (2417, page 1368), Gifford (2666), Strader (2766) and Awerbach (2801) (see §81 above).

Transitory edema of the eyelids is mentioned by v. Stellwag (235) in the case of a 20 year old female patient with Basedow's disease She suffered from frequent attacks of sharp stabbing pain spreading upward from the left temple During these attacks the left lower lid often became swollen, and a blue vein in the medial corner of the eye stood out After fifteen minutes the pain and the swelling disappeared Concerning

out protrusion of the eyes There was, however, an edema of the eyes and Chvostek adds that, according to his experience in this disease, edema of the eyelids occurs not at all infrequently Millard (780) reports an observation of Parinand, a peculiar swell-

tarsal region and sometimes extends as far as the lashes Nothing is stated concerning the duration of this swelling

year old girl with a swelling of both upper eyelids which preceded the first signs of the

disease and which remained after improvement in the other signs following a partial thyroidectomy Ingelrans (1591) reports a patient with Basedow's disease and edema of the eyelids Stratchley (1653) saw lid edema in the case of a woman who had suffered from Basedow's disease four and one half years Kocher (2197), as already mentioned above observed edema of the eyelids among such patients several times Among 52 typical cases of Basedow's disease which Landström (2849) assembled, edematous swellings of the eyelids occurred twice, in an 18 year old boy and a 19 year old girl In each case the whole face was markedly swollen A rather firm thickening of the subcutaneous tissue could be felt under the chin and on the sides of the neck

Sydney Stephenson (2440) reported a 12 year old boy who came for treatment of a

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Since the

A case of "iodine Basedowism" described by Breuer (1944) (675) was a female of 43 with edema of the lids and slight edema of ankles and shin bones This patient had no albuminuria

Among 95 cases which I, myself, observed I saw edema of the eyelids 4 times The girl of 19 described above who had small fibromas in the subcutaneous tissue (see §209 above) also had an edema of the upper lids three months after the appearance of the first distinct signs of the disease It lasted a few days, disappeared again, but, in the further course of the disease, occurred several times more in varying degree A woman of 52 whom I saw only once had edema of the lower lids An obstinate lid edema since the beginning of the disease, which she had had for about seven months, caused a woman of 25 with signs of Basedow's disease to visit the eye clinic Both upper lids were stretched like bags The swelling was not firm, a finger imprint did not remain, and the skin was of ordinary appearance The swelling varied, but never disappeared No noticeable protrusion of the eyes was evident

Intermittent Effusions of the Joints

§212. Closely related to acute circumscribed dermal edema is, doubtless, the intermittent joint effusion observed in rare instances among patients with signs of Basedow's disease Arising rather suddenly, without apparent cause, the swelling of the joints reaches its high point on the second or third day and then, after a few days, goes away again as rapidly as it came, sometimes after a few hours It recurs, however, at more or less regular intervals of a few days or weeks, seldom of one or more months, it returns again and again often over a long interval of time The swelling is only moderate, without redness, and without local temperature increase Interference with movement is usually negligible Pains are not great, but tend to be sudden and general Most frequently the knee joint is affected, sometimes also the elbow, or hip, more rarely the small joints are involved,

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[illegible]

out protrusion of the eyes There was, however, an edema of the eyes and Chvostek adds that, according to his experience in this disease, edema of the eyelids occurs not at all infrequently Millard (780) reports an observation of Parinand, a peculiar swelling of the eyelids among Basedow's disease patients This swelling affects the upper lids and fascia orbitalis Pressure of the finger leaves no indentation The skin covering is not stretched tight Small, enlarged veins show through This swelling does not cause the lid to take a deeper position But it forms a cushion which partly covers the tarsal region and sometimes extends as far as the lashes Nothing is stated concerning the duration of this swelling

Maude (992) observed, in 1 case of Basedow's disease, a swelling of the eyelids without other spread of the edema Gowers (1042) observed lid edema together with edema of the conjunctiva bulbi associated with only slight exophthalmia. H. Mackenzie (1614) stated that the edema-like swellings which occur in Basedow's disease appear most frequently on the eyelids, and sometimes on one eyelid only Usually it appears on both eyes, either confined to the lids or associated together with similar swellings on the lower extremities He mentioned 7 such cases Sometimes this edema is obstinate and remains when the other symptoms have disappeared Booth (1408) declared that edema of the eyelids is rare in Basedow's disease; but he observed a 17 year old girl with a swelling of both upper eyelids which preceded the first signs of the

disease and which remained after improvement in the other signs following a partial thyroidectomy. Ingelrans (1591) reports a patient with Basedow's disease and edema of the eyelids Stratchley (1653) saw lid edema in the case of a woman who had suffered from Basedow's disease four and one half years Kocher (2197), as already mentioned above observed edema of the eyelids among such patients several times Among 52 typical cases of Basedow's disease which Landström (2849) assembled, edematous swellings of the eyelids occurred twice, in an 18 year old boy and a 19 year old girl In each case the whole face was markedly swollen A rather firm thickening of the subcutaneous tissue could be felt under the chin and on the sides of the neck

Sydney Stephenson (2440) reported a 12 year old boy who came for treatment of a
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Since the
birth of a child eight months before she had become very nervous. The other Basedow's disease signs included tachycardia without noticeable palpitation, slight swelling of the neck and tremor. A swelling of dough-like consistency began directly under the eyebrows and extended to the upper tarsal border Strader's (2766) patient of 21 had just such lid edema and lacrimation as her first noticeable symptoms

A case of "iodine Basedowism" described by Breuer (1944) (675) was a female of 43 with edema of the lids and slight edema of ankles and shin bones This patient had no albuminuria

Among 95 cases which I, myself, observed I saw edema of the eyelids 4 times The girl of 19 described above who had small fibromas in the subcutaneous tissue (see §209 above) also had an edema of the upper lids three months after the appearance of the first distinct signs of the disease It lasted a few days, disappeared again, but, in the further course of the disease occurred several times more in varying degree A woman *of 52 whom I saw only once had edema of the lower lids An obstinate lid edema since* the beginning of the disease, which she had had for about seven months, caused a

Intermittent Effusions of the Joints

§212. Closely related to acute circumscribed dermal edema is, doubtless, the intermittent joint effusion observed in rare instances among patients with signs of Basedow's disease Arising rather suddenly, without apparent cause, the swelling of the joints reaches its high point on the second or third day and then, after a few days, goes away again as rapidly as it came, sometimes after a few hours It recurs, however, at more or less regular intervals of a few days or weeks, seldom of one or more months; it returns again and again often over a long interval of time. The swelling is only moderate, without redness, and without local temperature increase Interference with movement is usually negligible. Pains are not great, but tend to be sudden and general Most frequently the knee joint is affected, sometimes also the elbow, or hip, more rarely the small joints are involved,

usually on one side, sometimes on both sides. In the majority of cases which belong here intermittent dropsy of the joints was present for some time before the signs of Basedow's disease appeared. In 1 case (Loewenthal) these signs appeared only during the attacks and vanished with the retrogression of the joint swellings (see below). In another (Pletzer) the signs of Basedow's disease alternated with those of the intermittent joint dropsy (see below).

A woman of 29 was reported by Loewenthal (260) For the first time, and without apparent cause, she developed a swelling of the right elbow which lasted a few days and returned again at intervals of from three to four weeks These recurrent swellings of the joints occurred over half a year Three years later a similar periodic swelling began in the left knee joint, at first in intervals of four weeks and later of twelve days, recurring with mathematical precision Swelling and regression took five or six days In the intervals the joint was entirely normal and the woman felt no discomfort Only when the joint swellings were present did she complain of palpitation. She had tachycardia of 116 to 132 beats per minute Body temperature normal Bilateral exophthalmia and a staring expression (probably a retraction of the upper lids) were evident A thyroid enlargement could not be demonstrated and no examination seems to have been made for a tremor of the hands at that time (1871) With the reduction of the knee-joint swelling, the pulse rate returned to 72 per minute and the palpitation disappeared. Unfortunately, no report is given on the progress of the exophthalmia Loewenthal described a case as hygroma prepatellare From the description, however, there can be no doubt that, as in the other cases, it was an intracapsular joint effusion It was expressly stated that the patella moved about in the fluid

treatments, the general condition deteriorated The patient complained of palpitation and anxiety The pulse reached 130 to 160 beats per minute The thyroid gland seemed slightly swollen and the eyes protruded The woman soon became emaciated and had diarrhea every morning The joint swelling did not reappear Suitable treatment resulted in considerable improvement in the Basedow's disease Again, after an interval of four months, the swelling in the right knee joint resumed its earlier eleven day cycle Goiter and exophthalmia disappeared completely When a pregnancy occurred, the attacks of intermittent dropsy of the joints ceased Eight weeks after delivery the

right knee joint occurred

H Koster (1052) reports a case of intermittent joint disease affecting a woman of 27 *years of age who developed signs of Basedow's disease two weeks after* a slight sprain of the left knee joint Pain and a temporary swelling was followed without evident cause by a sudden much greater swelling which disappeared after having been painted with iodine After a month, another effusion followed which soon disappeared During the next five years the attacks of water on the knee recurred at irregu-

lar intervals without any special cause or stress on the knee Gradually the general condition deteriorated Nausea and vomiting began After puncture of the left knee joint, no more swelling occurred there Instead, at regular eight-day intervals and without known cause, swelling occurred in the right knee preceded by violent pains along the back of the thigh Subsequently, the right side of the face showed redness and heat, much sweating, polyuria, and enlargement of the thyroid gland Finally an intermittent effusion of both knees occurred Cardiac palpitation, exophthalmia and lid signs were absent

A case was observed by Homén (1013) for typical Basedow's disease, in the course of which intermittent swelling of joints occurred Homén had the impression that the effusion was less within the capsule than in the soft parts around the joint The swelling lasted only a short time and was accompanied by pain The intermittent joint involvement in this case was less regular than is usual

Pässler (1362) found, among 51 polyclinic cases, 2 in which joint enlargements had been observed Both times the swellings occurred in several joints (knee, foot and interphalangeal joints), and were painful but occurred without reddening or perceptible increase in temperature They arose without any discernible cause, lasted several weeks and disappeared again without any treatment Nothing is said concerning any recurrence of these joint swellings, perhaps because a more lengthy study of the ambulatory patient was not possible Oppenheim (2107 and 2417, p 1368) mentioned that, in 2 cases, he saw a "painful joint affection", with disappearance of the muscle in the course of Basedow's disease Temporary muscular atrophy has been observed several times, although rarely in association with an intermittent dropsy of the joints

§213. While I am grouping together the circumscribed dermal edema and the closely related intermittent swelling of the joints, the various vasomotor and secretion anomalies which we have encountered under accessory and secondary signs of Basedow's disease related to the angioneuroses, I am quite aware that this contributes but little to a closer understanding of these affections The apparent close relationship between the above cases of circumscribed dermal edema and intermittent effusions of the joints to Basedow's disease seem to me to exclude an accidental combination. Rather, it suggests a toxic influence analogous in action to many lymphagogues, which act gradually to produce such swellings in a series of attacks. Next it must be determined whether these substances exert their influence through nervous means or act directly on the walls of the capillaries in certain target areas to permit a quantitatively and sometimes qualitatively altered transudate to pass through, as for example by an enormous difference between the osmotic pressure within the blood or lymph vessels and that in the tissues.

Firm Swellings in the Skin

§214. Beside the transitory or lasting circumscribed or extensive dermal edemas described in §210, swellings of the skin sometimes occur in Basedow's disease which are of a firm elastic consistency and which offer

rather definite resistance to the finger pressure, such that only firm pressure of the finger can leave even a transient indentation. These edemas usually remain unchanged for a long time, or show slight variation. The localization is independent of the law of gravitation. These swellings most frequently affect the lower extremities, from about the middle of the thigh to the ankle joint, leaving the arch and foot free. Often, also the abdominal wall is affected. In rare cases such firm elastic swellings are arranged symmetrically in the grooves above the clavicle. Their consistency as well as their dull percussion note easily distinguishes them from the so-called lung-hernias which, at first glance, they seem to resemble.

This kind of dermal edema is more similar to that in myxedema. Aside from the different location however, there are also lacking, in true cases, all the other signs of this disease and the swellings are not at all or only very little influenced by thyroid treatment.

A swelling of both legs to the ankles and conspicuous emaciation of the upper extremities is mentioned by Eckervogt (516) in the case of a 42 year old woman Daubresse (540) and Dieulafoy (822) report similar cases Mobius (993) spoke of a Basedow's disease case under his treatment in which the skin over the peroneus muscle was swollen by edema while feet and ankles were not Signs of cardiac weakness could not be discerned V Jaksch (1045), in the Verein deutscher Ärzte in Prague, presented the case of a woman with typical Basedow's disease and an unusual enlargement of the lower extremities One gained the impression that the subcutaneous tissue contained a thicker substance than pure edema fluid The swelling was similar to that of myxedema, but all the other signs of that disease were absent On the other hand, an increase in the mechanical excitability in the facial nerve could be demonstrated, as in tetany (see §113) Joffroy (1117) observed one patient with Basedow's disease with a firm swelling of the lower extremities which extended up to the hips, but did not touch the ankles Five among Ditisheim's (1293) 17 cases from the Zurich clinic, suffered from a moderate thickening of the skin of the legs, especially over the lower legs, over this area, however, no imprint of finger pressure remained Ditisheim considered these changes as sclerodermic This, however, certainly was incorrect A 30 year old seamstress with hereditary nervous tendency was under Babinski's treatment (1264, Felix 1431) Simultaneous with the development of typical Basedow's disease signs a swelling of the ankles occurred, which gradually extended to the thighs. This myxedema-like swelling was firm but did retain an imprint from pressure, urine was normal Treatment with thyroid tablets brought no visible improvement during a course of three months A similar case observed by Low (1611) was a 23 year old woman with no hereditary tendency Almost simultaneously with the first signs

whole body and scattered vitiligo spots on trunk and extremities (see §202 above) The second case, a woman of 24, developed signs of Basedow's disease rather acutely, following an accident. Within a few months there was a similar swelling of the legs, and a loss of hair. Iodothyrin treatment was ineffective Deshusses (2280) reports a woman of 61 with severe Basedow's disease and a sizeable, firm, myxedema-like swell-

ing of the lower limbs A year before this had been confined to the calf of the leg Miesowicz (2516) observed a case of Basedow's disease with muscular atrophy of the upper extremities (see §134). The patient was 24 years old. In the subsequent course of the disease thickening of the skin appeared at the ankle-joints and later spread to the knees.

I have myself seen a peculiar, symmetrical thickening of the skin on both lower legs in the case of a 21 year old female Basedow's disease patient. I had opportunity to examine this case histologically.

The patient who apparently had no hereditary tendency gave a history of weak nerves from childhood. She was timid, and had developed slowly both physically and mentally The disease began four years before with swelling of the neck, palpitation, and increasing emaciation When I saw the patient for the first time the complete symptom complex of Basedow's disease could already be recognized, including a rather even, soft, elastic goiter, over which there was an audible systolic rushing *bruit*, but no thrill The neck's circumference was 33 cm There was pronounced exophthalmia (right 2 cm, left 20 cm) and a wide gape of the lid apertures The lids could, however, be closed completely Even with a partial closing of the lids the muscle sound over the lids could be clearly heard v Graefe's sign was present, that of v Stellwag absent, and that of Möbius present Visual acuity was normal. The ophthalmoscope made a slight motion of the retinal arteries evident There was distinct tremor of the hands. The patient perspired freely, complained of palpitation and shortness of breath, and displayed noticeable restlessness Her weight was 40 kg

About one year later a swelling which we shall describe more fully developed on the lower extremities

During this year the condition of the patient had deteriorated considerably The eyeballs protruded still more, and, because of the softness of the lids, no longer could be covered A red color appeared on the conjunctiva bulbi of the left then the right eye, this was followed soon by a purulent infection of the lower half of the cornea Three months after the beginning of the infection of the cornea the girl was brought to the eye clinic The lower cornea on each side was covered by an abscess Further extension of the infection did not occur, but a week afterwards there was a breakthrough of the right eye, four days later a breakthrough of the left occurred The process then gradually came to a conclusion by formation of a thick, non-elastic scar with a small ingrowth on the iris The upper parts of the corneas remained transparent and the pupils were only partly covered by the scars The eyes still protruded markedly, the right one 27 25 mm and the left one 26 5 mm, above the outer orbital border, v Graefe's sign was conspicuous However, retraction of the upper lids decreased and the eyes could now be closed The patient had been unusually emaciated

On admission to the clinic she weighed only 37 kg She felt weak and suffered from sleeplessness Concerning the blood tests, see §227 below With rest, suitable dietetic treatment, administration of sodium bromide and sodium phosphate, the general

surface to a trough-shaped cavity in the region of the ankle The involved area in-

creased in breadth from top to bottom The sides above the middle third of the leg were also affected Above the lower third the thickening affected the whole circumference of the leg Laterally it stood out from the healthy surrounding skin in a rather sharply defined line of separation, which ran from above medially and downward The medial boundary ran parallel in places The lower boundary was again definite

The skin changes were increased in every respect from above downward. Over the upper parts distinct, pimple-like elevations were evident, farther down these were wider, more crowded, mingled together in ring-like or bow shaped irregular masses. The isolated elevations ranged from quite flat to 1 mm high, nearly round, light rose colored or gray, shining like wax, and firm to the touch There were no scales The sweat secretion during the examination was noticeable in the region of this affection but less profuse than on the uninvolved areas of the lower leg More and more crowding of the mass over the lower third of the leg resulted in a coarsely papillated thickening Deep grooves separating the papillary excrescenses contained a stagnant fetid secretion The skin was thickened three- or four-fold It was movable over the underlying tissue Downward, the consistency became progressively more firm The color was a dull red

On the backs of the feet above the ankles, as already mentioned, the thickening [illegible]

An X-ray photograph taken at my request by Prof Perther showed some rather flat irregular thickenings, 1 to 2 mm high, in the upper third of the tibia, distinguishable from the cortical substance of the bone by somewhat lighter shadows Syphilitic infection had never occurred

No signs of venous congestion were present There were no discernible physical changes in the heart

In the subsequent course of the illness this thickening of the skin decreased. The isolated groups of lesions became flatter and the divisions were less distinct The skin took on a more livid red color and scaled somewhat at the surface

For microscopic study a wedge-shaped fragment from the middle and lower third of the altered skin was dissected and fixed, one part in Zenker's solution and another [illegible]

pulmonum

Pieces cut from the region of the greatest thickening, corresponding to the wart-like appearances showed an enormous development of the papillary bodies Since the epidermis partly filled the indentations, often deep, between the papillary elevations, the unevenness of the free surface was often much less pronounced than that of the corium Only a few papillae had a conical or cylindrical form Most were of irregular shape and rose 0 15 mm to 0 25 mm from a wide base The surfaces carried blunt conical or slender papillary eminences in varying numbers The wide superficial papillae reached a height of from 0 2 to 0 4 mm.

The epidermis over the papillae was only slightly heavier than the normal skin of this region (0 05 mm to 0 08 mm) From the depth of the indentations outward it measured, however, 0 1 mm to 0 45 mm in thickness The cornified layer was somewhat frayed in places. The innermost, cylindrical cell layer showed finely branched protoplasmic processes Between these delicate extensions of collagenous tissue with the thinnest of elastic fibers penetrated and provided firm anchorage between the epidermis and its under layer. In the invaginations of these, protoplasmic processes were

less distinct and resembled spindles such as can be seen at the basal boundaries of the cylindrical cells of the normal skin On the cells of the *stratum spinosum* spindle layers were clearly recognized It was not unusual to find sharply outlined vacuoles of 0 003 mm diameter in the cells, particularly in the spindle cell layer The nuclei were thin and pressed in half-moon form against the vacuole or remained within it as a chromatin-rich, clumped mass Karyokineses are found only exceptionally, but within the epidermis one often came across groups of cells which gave the impression of being younger elements

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tinct separation into fibrillae This became clearly evident by use of a Mallory-Mall stain to bring out the collagen tissues sharply In certain places the connective tissue *trabeculae* and lesser *trabeculae* no longer took the brilliant blue color, but displayed only a dirty yellow-brown color

The capillaries which passed into the papillae were distended, as were the small veins The vascular walls appeared unaltered Around most of these small vessels a narrow, open space was visible penetrated by a delicate net-work of connective tissue fibers and occasional elastic fibers These spaces were in open connection with the more or less greatly expanded tissue spaces in the deeper layers of the *pars papillaris* between the connective tissue trabeculae. The lymph vessels of this section of the corium had their own walls and were likewise enlarged

On the boundary between the *pars papillaris* and the *pars reticularis*, which in normal skin is not sharply defined, the edematous infiltration of the tissue was extraordinary The so called Langer's rhomboids were enormously enlarged as were the connective tissue trabeculae which crisscrossed in all directions and seemed to be separated by fluid into smaller and smaller bundles (0 005 mm to 0 002 mm thick) and into single fibers, and separated in a wide meshed network The bundles and fibers were not wavy but curved, or stretched by the fluid The stronger connective tissue trabeculae gave a more homogeneous appearance In the area of the sweat ducts, of the roots of the hairs, and of the larger vessels a somewhat thicker connective tissue remained The coarse elastic fibers stood out plainly (with special staining methods) between the connective tissue trabeculae The finest fibers in the papillae, as already mentioned, could be followed into the furthest extensions of the connective tissue and between the basal processes of the columnar cell layer where they were less well stained than in the control preparations of normal skin

The edema fluid was evidently albumen-poor and mucin-free

The connective tissue cells were in most cases of normal appearance The nuclei of several stained poorly in the region of the greatest edema In preparations stained by the Pappenheim method the region of the deeper, looser layer of the *pars papillaris* contained plasma cells which seemed to have been in amoeboid motion at the time of fixation

In the neighborhood of the smaller vessels were many mast cells but few leucocytes with round or lobate nuclei

Where small nerve bundles were encountered in the section, no change was noticeable

The small hairs and follicles varied from normal only in that the cornified layer of cells extended deeper, and outwardly many of the cornified cells had frayed off The sweat gland ducts showed a peculiar alteration The lumen was very unequal in width and more widely open than is normal. In a few the lumen has a diameter of from 0 008 mm to 0 015 mm Exceptionally it reached 0 02 mm in one direction and 0 03 mm in

the other The normal width is 0 003 mm to 0 004 mm The cellular wall adjoining the lumen was 0 003 to 0 006 mm wide It was homogeneous, as if swollen tightly, and often irregularly curved The cell boundaries had almost completely vanished. The intercellular matrix had taken on a dark color The nuclei were in the basal portions of the cells, they were pale and poor in chromatin. The change we are describing extended to the portion of the duct which lies between the epidermal cells Only very few sections of the secreting, coiled regions of the sweat glands were available on the slides Here also the protoplasm of the epithelial cells toward the lumen had a more homogenous appearance and the cornification was less distinct In many cross-sections the lumen was not circular but bounded by a peculiar line bending in and out

The above described alterations of the sweat glands may well have been caused by the peculiar skin edema In the sample of skin from the same region of the 42 year old male patient (see above) the sweat glands had an entirely normal appearance I

were smaller, the papillae were mostly plump, conical, occasionally slender, and had an elevation of from 0 025 mm to 0 07 mm A few rose to 0 12 mm and were capped

space The connective tissue bundles were spread apart to form a wide meshed network of fine threads Only toward the subcutis did the bundles draw nearer to each other and the larger trabeculae become more numerous Here, also, they were of a peculiar homogeneous appearance

These results of the histological investigation present evidence that an exudation of fluid into the deeper layers of the corium is the basis in the firm, more stable or lasting dermal swellings Since all signs of congestion in the veins are absent and, since there is no reason to assume an obstruction of the efferent lymphatics, we have to attribute fluid secretion to the angioneurotic edemas H. Meigl has named this trophoedema I am quite aware that such names contribute little toward an understanding of the pathogenesis of this occurrence. It cannot be stated how far nervous influences play a role here. Perhaps damage to the walls of the capillaries and small veins, resulting in increased permeability accounts for the change This might perhaps be caused by toxic influences acting selectively. The anatomically demonstrated changes in the orbita following paraphenyldiamine poisoning are those of an acute and rapidly disappearing exophthalmia which may appear in the fatty tissue of the orbit as a result of toxic action (cf A. Birch-Hirschfeld; this book, 2nd ed. part II, vol IX, chapt. XIII, §145).

In a number of other cases not only the lower extremities are involved by these swellings but the abdominal wall also.

An exceptionally perfect case of this sort was described by v Basedow himself (15) in his first report on the disease named after him A woman in the middle of her twen-

demonstrated The lower extremities from the lower third of the thighs were tremendously enlarged but not obviously edematous. Instead, the tissue seemed engorged by a plastic jelly. Finger pressure left no indentation. Puncture of the skin produced no flow of serum Swelling on the feet and fullness of abdomen, almost resembling pregnancy, still remained when the disease had improved and the woman had regained "quite endurable, relatively good health" Of a 50 year old male, v Basedow stated that, although there was great emaciation, the body remained stout and the cell tissue in the knee joints and calves appeared stiffly swollen, though there was no edema of the feet Vogt (370) observed a 30 year old unmarried woman who had typical Basedow's disease signs with edema of the lower extremities and abdomen Edema and goiter disappeared before death which occurred after six years Concerning the nature of the "edema" nothing further is explained.

J P Mobius (993 and 994) described a representative case of this sort A 50 year old patient with Basedow's disease with a weakness of the heart was extraordinarily emaciated, arms were only skin and bones, face sunken, and thorax, so to speak, skeletonized The lower half of the body was edematous This edema was slight on the feet, but from below upward it increased and was greatest over the abdomen It ceased entirely above the naval This swelling burdened the patient greatly and necessitated repeated incisions in the wall of the abdomen No peritoneal effusion was discovered The edema lasted until death occurred three months later Nothing is stated about the consistency of the swellings Canter (1183) observed a patient with pronounced signs of Basedow's disease Abdomen and legs were locations of a peculiar, firm edema Thyroid treatment reduced the swelling, while tachycardia, tremor excitability and perspiration increased H Mackenzie (1614) reported a firm swelling of abdomen and legs, suggestive of myxedema, which sometimes occurred among Basedow's disease patients, and which did not yield to thyroid treatment Murray (1891) reported that he sometimes had observed a firm subcutaneous swelling on several parts of the body in Basedow's disease and added that it certainly was not of the nature of myxedematous swellings Achard (1933) demonstrated, in the neurological section of the International Congress in Paris, a woman with a firm myxedema-like swelling of the skin of the lower extremities and of the abdomen The patient had suffered from Basedow's disease for sixteen years Three years previously Faure had undertaken a bilateral section of the cervical *sympathicus* After brief improvement the goiter increased and so did exophthalmia, tremor, frequent diarrhea, skin pigmentation, the vitiligo (see §202 above) and a swelling of the skin resembling pachydermia v Mikulicz and Reinbach (2010 and 2103) observed a 46 year old man with severe Basedow's disease and edema of the abdominal skin and the skin of the lower extremities, which was "as hard as a board" This edema disappeared after a partial

to protrude The upper part of the body became greatly emaciated in spite of a voracious appetite Other signs included nervous unrest and sleeplessness

A case from the Ziemssen Clinic as reported by Bodensteiner (2045) appears to belong here A woman of 24 had clearly developed Basedow signs and swollen face with

an infiltration of the subcutaneous tissues, especially in the region of the parotids There was enormous thickening of the skin of the abdomen and deep transverse folds with firm ridges at knee joints, elbows, and backs of the feet. The skin in these places was soft and pale In certain places on the lower extremities infiltration as hard as thick leather appeared. Here it was also slightly pigmented with brown, deep transverse folds and wide hair follicle openings could be recognized

A woman of 24 with Basedow's disease was described by Laignel-Lavastine and P. Thaon (2526) The skin on the lower half of the body was thickened and hard The goiter and the dermal thickening seem to have been present before the appearance of the other signs of Basedow's disease

The communication of L v Schrötter (2344) is of special interest It concerns a typical case of Basedow's disease, a woman of 27 with extensive pigmentation of the skin and conspicuous firm swelling of the whole lower half of the body. He acquainted us with the results of an anatomical study of the substratum of this swelling The skin could be lifted up on face, neck, breast, upper extremities, and abdomen, a *panniculus adiposus* was entirely lacking The lower parts of abdomen and legs appeared unusually large The skin in this region was so firm that it hardly showed an impression from finger pressure Such pressure did not leave an indentation anywhere. It was possible to raise up a small fold in one place only Also, as in the above-men-

2 weeks was discovered; this was followed by a decrease of 7 cm in a period of two months The increases and decreases occurred by no means simultaneously in all parts of the swellings While the aforementioned increase in size of the thigh was taking place, the thickness of the hips had decreased by 2 cm

In order to permit a conclusion as to whether it was a change in the skin analogous to myxedema or some other alteration, two good sized pieces down to the fascia were removed from the thighs under anesthesia. These made evident even macroscopically

single fat lobules were larger than those seen under normal conditions In the cutis and its papillae and in the blood vessels nothing abnormal could be seen The examination of the chemical composition of the fatty tissue, as made by Panzer (2961), showed no difference between the fat of the mammae and that in the region of the lipomatosis, and also no essential difference from the results of other investigators of subcutaneous fat

It is, therefore, a lipomatosis confined to the lower half of the body. L.v. Schrötter believed, I think correctly, that in many cases of other observers where such a hard swelling confined to the lower half of the body or any other sign of myxedema was present, it must have occurred in the same way.

This holds true, probably, for the case of Möbius described in 1891 (see above). Although Möbius, in 1896, stated that water exuded where cuts were made on the abdominal wall, that still does not prove, it seems to me, that the whole swelling is to be attributed to a collection of fluid in the subcutaneous tissues Since the woman suffered from a weak heart, an edematous saturation of the abnormal fat accumulation in the subcutaneous tissue should not cause any surpr

General adiposity has been observed several times with swellings and tumors of the hypophysis. Perhaps, in these abnormal subcutaneous fat accumulations confined to the lower half of the body, an affection of the hypophysis plays a role

Skin swellings of this sort should not be considered definitely angioneurotic edema, but should be related to the metabolic and nutritional anomalies which are characteristic of Basedow's disease and with which we shall deal later on. Variations in intensity such as occurred in v. Schrotter's case, are not uncommon in the general metabolic disturbances during Basedow's disease. Perhaps the same anatomical causes lie at the bottom of the above mentioned hard, non-painful swellings, resistant to finger pressure, located in the *fossae subclaviculares*

Rendu (565), to the best of my knowledge, first called attention to this, and Sainte Marie (736) described such a case of a 47 year old woman under the title *Pseudolipome sus-claviculaire combiné à la m de Basedow* The patient, who had recently entered the menopause, had always been well She sought medical help because of a feeling of strangulation in the throat, and a shortness of breath There was a symmetrical goiter with a distinct *bruit*, carotid pulsation, pronounced exophthalmia, congestion in the face, cardiac palpitation, and a slight tremor of the hands There was a hump-like protrusion which felt like a firmly stretched lipoma in the hollows above the shoulder blades on each side Kocher (2197) saw a 20 year old woman who, in the *fossae claviculares*, had small hard elastic swellings such as occur in myxedema, although no other symptoms of this disease were present

§215. In this connection we must direct attention to the combination of Basedow's disease with Dercum's disease, the so-called *adipositas dolorosa*

The first case of this kind was reported by Johanny Roux (2227a) A woman of 57 had the typical signs of Basedow's disease and a number of small swellings which had appeared several weeks before on both lower arms They gave the impression of encapsulated lipomae One of these was soft like dough and somewhat painful under pressure This seemed to be a condition of connective tissue thickening. When the arms were used or the areas were rubbed there was a mild pain in the swellings

A Ghelfi (2376) observed a 54 year old female who had general adipositas, and almost symmetrically arranged lipomatous nodules on the forearm and on the buttocks. The skin over them was sensitive, but pressure on the fatty masses caused no appreciable pain Besides these signs there was tachycardia, moderate goiter, a tremor and a slight exophthalmia of the left eye

Giulio Fratti (2823a) also described a case of Dercum's disease in which conspicuous signs of Basedow's disease were present

Dercum himself and several other observers suggested the possibility that an alteration in the thyroid gland in the nature of insufficiency of function might be the basis for the peculiar symptom complex (see Combination of Basedow's disease with Myxedema Signs, §221) In several cases, also, thyroid-gland treatment has been helpful. More frequently it was unsuccessful Once Dercum found alterations in the hypophysis (an epi-

thelioma) and new formation of lymphatic tissue in the fatty masses while the thyroid gland was intact.

Erythromelalgia

§216. In one case that extremely rare condition, named erythromelalgia by Weir Mitchell, has been encountered in combination with Basedow's disease Engelen (2821) reported a male of 20 who consulted him because of painful parasthesia in the hands. This pain recurred at intervals. During these attacks the hands took on a purple red coloration with scattered cyanotic areas In the intervals between attacks the hands showed a moderately red color Upon observation of the hands, furthermore, a rapid tremor was noticeable Under further examination a soft, insignificant goiter was discovered. There was also a paroxysmal tachycardia. Usually the pulse rate was only about 78 beats per minute. Exophthalmia was not present, but Graefe's sign was evident in fully developed form. The symptom complex was then completed by a marked sweat secretion on hands and face and a certain motor weakness. Although these latter signs as well as tachycardia have repeatedly been observed as accessory signs of erythromelalgia, there can be no doubt that the present case is a combination of this disease with Basedow's disease

Sclerodermia

§217. Sclerodermia is another disturbance to be listed among the so-called troph
tissue, and wh
dow's disease
spotty form The former afflicts, preferentially, the face and the hands, especially the fingers Sometimes it extends over neck, upper chest and back, more rarely the feet are also affected In exceptional cases the process is localized on the lower extremities only. Usually the cases come under observation only during the uncommonly characteristic and unmistakable indurated stage, rarely in the preceding stage of hard elastic swelling, which is usually of short duration, in which there is a certain resemblance to the conditions described in the preceding paragraphs.

v Leube (315) was the first to describe the combination of sclerodermia and Basedow's disease A 36 year old woman had a goiter since she was 20 and Basedow's disease for nine years Exacerbation of the disease occurred after a difficult delivery. At the same time the changes in the skin of the face and hands began which v Leube had an opportunity to observe six months later. The skin in these places was smooth, and hard to pull up into folds, the pulled up fold was hard and the patient had a

feeling as if, during movement, the skin was too tight Improvement of the Basedow's disease produced a favorable change in the skin disorder

A 30 year old woman without any hereditary tendency had Basedow's *disease*, a troublesome pulsation in the abdomen (see §14) and lameness with attempted flexion of the lower extremities (§124). O Kahler (775) found distinct signs of skin *sclerodermia on the legs, similar to that described by* v Leube.

Two typical cases were contributed by Sainte-Marie (736). The first, coming under the observation of Balzer, has already been described in a thesis about sclerodermia by Bouttier The case, a woman with Basedow's disease, showed *distinct sclerodermic* disorders in face and fingers The second case was a woman *of 52 without a hereditary tendency* This patient from the clinic of Langereaux had a goiter and cardiac palpitation During several pregnancies the goiter increased in size but caused no difficulty otherwise With the climacteric pains occurred in the shoulders and fingers, also a slight swelling of the latter, and almost uncontrollable vomiting *In three months the* whole symptom complex of Basedow's disease had arisen, *only the tachycardia remained moderate* At this period of the disease the face had taken on a mask-like expression. The features were motionless, the skin of the jaw, temples, and lips was smooth, shining like wax, and like parchment The hair of the scalp was intact. The tongue became difficult to move Only its tip could be brought to the mouth opening The skin over the bones *could hardly be moved and felt as if attached to the* smooth places There was no disturbance in *sensation* The hands *displayed sclerodactylia*, they felt cool. Violet spots showed on the fingers when the surrounding temperature was low The nails were ridged lengthwise

A similar case was observed by Jeanselme (1213) A woman of 53 from Strassburg contracted an obstinate dysentery while in Brazil In the course of this illness a goiter, which she had had for some time, rapidly increased in size This reached the size of an orange, it was hard, non-pulsating, and occupied the right lobe of the thyroid gland There was slight exophthalmia, moderate tachycardia, subjective *sensation of palpitation, and distinct tremor under excitement Five or six years later*

the skin was only slightly moveable over the underlying bones The nose was sharp and narrow The nostrils had lost their natural roundness, the lips were thin and wrinkled The skin of the cheeks seemed somewhat hardened The neck and the upper chest region showed the beginning of sclerosis The fingers were bent inward toward the palms and peculiarly deformed The tactile and temperature sensitivity in the affected parts was somewhat reduced and these areas felt cool and dry to the touch. The skin of the backs of hands, neck, upper part of the trunk, and of the lower abdominal region was pigmented

Jeanselme also reports a second case which has been published in a thesis by Machton A 51 year old woman had a goiter for about 20 years At the climacteric it began to grow much larger and showed *daily changes in circumference but no pulsation* A tremor appeared in the upper extremities Nélaton removed a goiter cyst by surgical means, and of this a fistula remained After that the patient became greatly emaciated, was unusually excitable, perspired profusely, and had almost daily nosebleeds Tremor increased and the eyes protruded At this time the skin of the forehead seemed indurated, smooth and shining, and could scarcely be moved about on the underlying bones The skin over the jaw was thickened, as well as that over the breast bone and below the clavicles. The upper extremities were still free, but the legs showed hard, elastic swelling from the knee joint to the insertion of the Achilles tendon

A woman of 32 reported by Samouilson (1782) had suffered from Basedow's disease for ten years Five months before being seen she first noticed that the skin of her forehead was less movable, it looked smooth, shiny, of a yellowish brown color and could not be wrinkled. A sclerotic spot was noticed on the right nostril. A therapeutic test with thyroid tablets produced violent attacks of tetany

E Dupré (1956) showed a woman of 34 with a marked hereditary tendency. At the age of 13 the first signs of Basedow's disease had appeared They soon reached full development Ten years later signs of sclerodactylia appeared on the two last fingers of the left hand In her 29th year she had frequent attacks of tetany (see §113, above) At the time of the demonstration she showed considerable exophthalmia, strong retraction of the lids, moderate goiter, pulse of 110 to 115, definite tremor of the hands, and atrophy of the breast glands. She had almost daily attacks of diarrhea Furthermore, the skin of the forehead appeared smooth. It could not be raised in folds or moved about on the underlying bone structure On the hands the sclerodermic changes affected the fourth and the fifth fingers The affected places showed reduced sensitivity to touch and pain while temperature sensitivity was retained

At the Natural History Medical Association in Heidelberg, Krieger (2305) presented a woman of 58 who had been healthy and strong up to her 44th year, but who had experienced great anxiety and trouble recently and had developed costal pleurisy.

improved, but two months after that the eyes began to protrude from the orbits. The exophthalmia soon diminsished again But it was followed by the development of a large goiter which was soft and pulsating Even at that time the woman had noticed a bluish discoloration at the tip of the right index finger This occurred each time after exposure to cold and was accompanied by great pain In the following year this change extended to all the phalanges of the second to the fifth finger Later the left hand was affected in the same way Gradually, a swelling of hands and fingers developed which soon became permanent Recently the disease had extended to the

the lower extremities, the skin on the lateral aspects of both lower legs felt somewhat

but the sclerodermic changes came out very distinctly and spread to the middle of the fore arms and to the knees The skin of the face now appeared somewhat thickened and less movable

Changes in the fingers which, perhaps, may be designated sclerodermia, were found by Kocher (2197) in 9 among 80 cases of Basedow's disease The fingers appeared thin and pointed

A 29 year old male seen by A. Fuchs (2357) was presented in the Verein für Psychia-

trie in Vienna The typical signs of Basedow's disease had developed a year before Seven or eight months later painful swellings on the lower legs developed and regressed in the course of a month. But on the anterior surface of the lower legs they became harder and harder. The skin here was transformed into stiff hard layers which stood out rather sharply above the surrounding areas. The skin over these areas was shiny, and pigmented with a slightly brownish coloration. Hair growth here was more scant and sensitivity reaction less prompt.

There are several other cases in which the disease began with the symptoms of scleroderma dominating the clinical picture. The more or less completely developed signs of Basedow's disease were only discovered by more thorough examination.

In 1894 B Beer presented a patient before the Vienna Medical Society The signs of scleroderma, exophthalmia, and tachycardia were present A 28 year old woman presented by Wick (2792) before the Vienna Medical Society had acquired parasthesia of the hands one year after a severe influenza with costal pleurisy This was followed by abscesses of the nails and loss of the nails Two years later the fingers became bent and the terminal phalanges shorter. Later, the same changes occurred *in the feet The skin was smooth and tightly attached to the underlying layer* and the nearly immovable finger joints were excoriated and ulcerated The skin on the wrist joints was similarly affected From here, with increasing intensity, the process spread up to the upper arms From the feet the alterations spread up to the knees The mouth could not be opened easily and there was a certain feeling of stiffness in the jaw movements The teeth had partly been lost Furthermore the eyeballs protruded, the thyroid gland was slightly enlarged and the pulse rate was 80 per minute At the next sitting of the Vienna Medical Society F Kornfeld (2694) demonstrated a 31 year old woman without any hereditary nervous tendency She showed a combination of scleroderma, which had developed unusually rapidly, with a tachycardia of 100 to 130 beats per minute, a wide gape of the palpebral fissure, infrequency *of blinking, and insufficiency of convergence Outwardly no goiter was evident, but* by palpation a knot the size of a small nut could be felt lying on the trachea The disease had begun, a year before, with a feeling of cold in the finger joints and tips of the toes, parasthesia, and a bluish-red discoloration of the fingers Along with the spreading of the sensations of cold, and the parasthesias over the upper and lower extremities, a progressive thickening and hardening of the skin took place extending over the hands to the upper arms, chest, neck and face As in the previous case, there was a tendency to develop painless, small abscesses, the size of peas, on the finger joints and elbows, all showing little tendency toward healing During the past year the teeth had rapidly become carious By much massage and regular use of thyroid gland tablets a distinct improvement followed, while the skin became *more pliable and the stiffness of the fingers diminished* Kornfeld was hopeful of still greater improvement A 39 year old woman, observed by R Freund (2661) had the typical signs on the arms and face after she had, for several previous years, suffered from joint disorders Then came pigmentation of the skin, muscle atrophy, palpitation, marked sweating, and a small goiter with a distinct *bruit* Bloch & Reitmann (2618) mention briefly a scleroderma in the case of a female patient who showed the signs of a typical Basedow's disease

Revilliod (1373) mentioned a case in which, beside menorrhagia and attacks of

phosphaturia, painful lumps on the fingers and sclerodermia occurred (see §219 below)

In 3 among the cases of sclerodermia with Basedow's disease which have come to light, the first one appeared in a circumscribed form

A 33 year old woman whom Grunfeld (1445) observed had developed the symptom complex of Basedow's disease quite rapidly six years before. After two years the manifestations disappeared almost completely Yet two years later they appeared once more in a severe form Within a short time the patient lost 10 kg. At about this time several brown spots appeared on the back of neck, throat and chest. During temporary improvement of the Basedow's disease such spots appeared along the spine and at several other places on the trunk, partly in the form of brand-like stripes. The skin in these places appeared dry, hard and of a dirty yellow-brown color. In the centers it was immovable and shiny Sweat secretion, temperature and sensitivity were reduced in these places Thyroid tablets resulted in improvement, first of the Basedow's disease signs, then in the sclerodermic changes also Finally, most of the patches disappeared without leaving a trace, and no new ones appeared Except for a slight protrusion of the eyes, the Basedow's disease seemed to be cured

Sittman (1917) mentioned, without any exact description, a case of disseminated sclerodemic patches in Basedow's disease with secondary myxedema. Peterson (2562) demonstrated, to the New York Neurological Society, a 15 year old girl with Basedow's disease, sclerodermic spots on the trunk, and circumscribed bald patches on the head

It is certainly no accident that, with one exception, all the cases of sclerodermia in Basedow's disease known up to now have been women; for we know that both diseases are more frequent in the female sex. The patients affected by the diffuse form are between the ages of 29 and 58. A hereditary tendency was emphasized in only one case (Dupré), in two its absence was mentioned; in the others no mention of it is made. In the majority of the cases Basedow's disease preceded the sclerodermic signs by from one to ten years, once by only seven or eight months. In 3 cases the manifestations of both diseases broke out at about the same time (in Sainte-Marie's second case, in the second case of Jeanselme, and in Krieger's 58 year old female patient) In one case (v Leube) development of the sclerodermia was concurrent with exacerbation of the Basedow's disease after a difficult delivery; in Grunfeld's case, it came with a relapse of the Basedow's disease In 2 cases, one of Sainte-Marie's of a 52 year old woman, and one of Jeanselme's, of a 51 year old woman, the approximately concurrent development of both diseases came during the time of the climacteric. In Krieger's 58 year old patient it was preceded by much trouble and anxiety and pleurisy. In the other cases no apparent cause for the occurrence of the sclerodermic changes was evident.

A certain close relationship of the two diseases to one another should not be considered out of the question. This seems to me to be substantiated

by the circumstance that in several cases (v. Leube, Grunfeld) a remission in the Basedow's disease signs was followed by improvement in the sclerodermic manifestations

G. Singer (1246) was probably the first to express the opinion that scleroderma is connected with pathological alterations of the thyroid gland and a disturbance in its functioning, and that myxedema, Basedow's disease, and sclerodermia represent related disease processes. He based this belief on the discovery of a considerable reduction in size of the right thyroid lobe, and a knotty thickening of the left one in a case of sclerodermia involving a 57 year old woman, as well as on a certain resemblance of the signs which sclerodermia shows in its first stage to those of myxedema. The substance of the right thyroid gland lobe in the case referred to seemed coarsely lumpy and dark-brown and microscopic examination showed an extensive connective tissue growth together with much shrinkage. In a second case of sclerodermia a delicate tremor of the hands as in Basedow's disease was evident In the case of a patient with sclerodermia presented by Beer in 1894, enlargement of the thyroid gland with atrophy of the parenchyma was shown. I bring to mind here the case of Sittman's (p 320) briefly mentioned above, with sclerodermia "en plaques" and Basedow's disease in which, later, the signs of myxedema appeared. Also the cases of Dupré and Samoulson (see above) in which patients with Basedow's disease and sclerodermia had violent attacks of tetany Among the French writers, Brissaud (1277), Jeanselme, and Dupré are inclined to attribute an intermediary rôle to the thyroid gland since intoxication of certain parts of the nervous system, caused by a definite disturbance of its function, can produce a trophoneurosis under the pattern of sclerodermia, just as in other cases it causes pigmentation anomalies of skin, falling hair, etc The cogent arguments of Nothnagel, Strümpell, Roux, to which others have been added recently, speak in support of the assumption that sclerodermia is caused by a disturbance of an inner secretion The last two authors direct attention to the hypophysis A favorable influence of thyroid-gland treatment on sclerodermia, observed several times, must be designated as not yet certain at least.

Raynaud's Disease

§218. In the above case of sclerodermia (§217) in Basedow's disease which Krieger (2305) observed, the disorder of the fingers began with signs corresponding to the initial stages of Raynaud's disease, the local asphyxial changes (Handbuch der Augenheilkunde—2nd ed vol. IX chapt XIV) In this case the fingers did not become grangrenous A combination of this disease with sclerodermia has been observed a few times.

P J Mobius (1478) stated that he had seen goiter in Raynaud's disease, and also certain Basedow's disease signs. In extremely rare cases a symmetrical gangrene appears which, in all cases known up to now, affected large parts of the limbs or extensive areas of the skin. That this extension of the necrosis, only observed in exceptional cases of Raynaud's disease, is the rule in Basedow's disease, according to observations available up to now, may be explained by toxic damage to certain parts of the nervous system according to the severity of the disease, the profound disturbance of the general metabolism, and the diminished resistance of the tissues resulting from the latter. Nobody will doubt that a spastic condition of long duration is a sufficient explanation of the manifestations.

Among the 5 carefully described cases, 3 ended in death In one case a typhus infection came first, following this signs of local asphyxia became evident Four cases were females between 45 and 58 years of age. It is quite possible that arteriosclerosis of the smaller branches favored the development of gangrene. However, the normal appearance of the artery wall has been emphasized expressly several times. It seems to me well founded, that the gangrene in the Basedow's disease cases we are considering is to be considered a severe form of Raynaud's disease, on the one hand because of its symmetrical arrangement and on the other because of lack of other sufficient causes, especially lack of arterial lesions The majority of cases belonging here have, furthermore, first come under study at the stage of well-developed gangrene, so that the initial signs have been withheld from observation

The first information about symmetrical gangrene in Basedow's disease came from Marsh (17) in the year 1842 A woman with unmistakable signs of Basedow's disease die

the [illegible]

quite unexpectedly was attacked by extensive gangrene of the left leg. Later the indication of the beginning of necrosis appeared on the right foot and the left hand. She died soon afterward The corresponding arteries were found to be occluded, but "the arteries themselves were entirely healthy" Otherwise, the results of the dissection were entirely negative

A case observed by Rabejac (232) was a 53 year old female Basedow's disease patient in poor circumstances Gangrene developed in the lower extremities and death followed The autopsy was negative

A 43 year old female patient of Hay (975) had suffered from Basedow's disease for three years. Symmetrical gangrene developed in both feet, on the abdominal wall and [illegible] the trochanter The patient gradually became feeble-minded.

[illegible]

sclerosis of the nerves and blood vessel walls

Thompson (2213) observed the typical case of a 29 year old male with a marked hereditary tendency, he had had the classical signs of Basedow's disease since he was 9 years old Following a typhoid attack regional asphyxiation signs occurred. Soon afterward the left arm developed gangrene and had to be amputated The patient refused food, attempted suicide, fell into delirium, and died

A Piazza (2960) reported a case in which, in the twelfth year of life, a completely developed symptom complex of Basedow's disease was combined with a probably characteristic Raynaud's disease dating from the ninth year

Osteomalacia

§219. The combination of Basedow's disease with osteomalacia is rare. Sometimes it is only a matter of slight bony deformities, of moderate kyphoscoliosis or knock-knees, or of a slight sensitivity to pressure on certain places on the spine, so that the diagnosis of osteomalacia cannot be made with certainty during life and can only be made by an autopsy But we cannot avoid the conviction that a close relationship exists between Basedow's disease and osteomalacia if we gather the few observations contained in the pertinent literature and combine them with a series of facts to which Hoennicke (2512) has recently drawn attention in his very thorough studies This investigator has shown: 1. that osteomalacia in its geographical occurrence is confined to the goiter regions, 2 by analysis of numerous osteomalacia cases, he has found that many of these have a goiter even though it may be only small. In cases where certain evidence of thyroid enlargement could not be found, goiter occurred in the family 3. He made the important observation that not only in osteomalacia patients with goiter but also in those in whom a thyroid gland enlargement could not be discovered, signs are present not infrequently which also occur in the symptom complex of Basedow's disease: congestion in the head, dizzy attacks, palpitation, trembling of the type of P Marie's tremors, diarrhoeas, and, in a few cases, sweating and polydipsia also Hoennecke has tried to make it seem probable that these symptoms, when they occur in osteomalacia, are of thyroid origin, and are not explained satisfactorily by the other disease symptoms or some previous operation (castration).

Latzko (2093), in agreement with Fehling's view, which has many followers, concerning the pathogenetic significance of the ovaries in osteomalacia, has expressed the view that not only osteomalacia but also Basedow's disease, when occurring in this combination, must be attributed to an inner secretion of the ovaries as the source of the illness In view of the indisputable close relationship existing between the thyroid gland and the female reproductive process, to which we shall return later, he believes that a fundamental mutual exchange relationship must be assumed to exist between the internal secretion of the ovary and that of the thyroid gland, so

that a disorder in the functioning of the one may have, as a consequence, a disorder in the other also Revilliod (1373), who has expressed himself similarly about the relationship of Basedow's disease to osteomalacia, called attention to the phosphaturia which also occurs in Basedow attacks sometimes He found it in 7 of 14 Basedow cases

The first case of a combination of Basedow's disease and osteomalacia was described by v Recklinghausen (1001) Koppen's (1051) 23 year old female patient had suffered from typical Basedow's disease for five years. Later she complained of pain from pressure on the lower neck vertebrae and upper thoracic vertebra The patient had already noticed a slight kyphoscoliosis *for the past two years* At the last she complained of pains in both arms She died quite suddenly in the night, after being quite well the day be
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Here is added a case observed by Hoennicke (2502) It is of special interest, since it is the only one of a male The 47 year old patient from Lausitz, in Saxony, was received in the Royal Saxony Insane Asylum, of Sonnenstein, because of states of excitement and irrational illusions Up to about eight years before he had been healthy, industrious modest and shy *For four years he had developed a thickened neck* and goggle eye
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chiefly behind the
A case reported l
Basedow's disease.
death, and extremely soft bones The hyperostotic skull bones contained diploe everywhere; the inner layer was thin, slightly rough, and allowed the cutting of good sections.

In the following 11 cases, osteomalacia was discovered during life.

Fr Moebius (1885) reported a female of 48 from Damsch's Polyclinic Five years *before, following a great fright*, she had developed the signs of Basedow's disease in rapid succession At the same time signs of myxedema appeared which during the later course came more into evidence (see §221 below) Since her last delivery, six and one half years before, she had complained of pains in the back, in the pelvic girdle bones, and the ribs, and had noticed that her clothing had gradually become too long The gait was conspicuously wobbly *The pelvis was unusually wide, and the sacrum* convex When the two iliac crests were pressed toward one another from the sides, the patient reported sharp pain sensations There was slight lumbar lordosis Pressure on the floating ribs from the back, close to the vertebral column, was painful The finger tips reached to the upper edge of the patella when the arms hung loose Weintraud (2789) mentioned Basedow's disease with subsequent myxedema (see §221 below) in the case of a woman who later developed osteomalacious changes in the skeletal system. Together with a diffuse calcium deficiency of the bones recognizable by their transparency for X-rays, they showed, by radiography, a peculiar resorption process of both ulnas, one scapula and several metacarpals Weintraud thought that these changes were caused by fractures Repeated X-ray exposures showed absolutely no callus formations at these fracture areas

Latzko (2093) adds the following concerning 5 observations of Basedow's disease with osteomalacia In one case typical tetany was present In a sixth case, a woman of 38 who had never had a puerperium, osteomalacia had been present for nine years and tetany for eight years Basedow's disease signs were not specified here

phosphorus treatment the latter was cured and signs of Basedow's disease diminished spontaneously A delivery in the past year brought on no relapse A woman of 36 had developed a goiter rather quickly ten years before during confinement In the following two years she lost 20 kg and had heavy perspiration but no palpitations Seven years later the osteomalacia developed. A facialis phenomenon was also distinctly recognizable, but there was no real tetany. Under phosphorus treatment considerable improvement in the osteomalacia resulted In the 2 following cases osteomalacia preceded the Basedow's disease A woman of 32 had osteomalacia for seven years For four years, from the beginning of a pregnancy, she had Basedow's disease and tetany (see §113 above) An irregular course of phosphorus therapy brought about improvement in both diseases For three years no more tetany attacks occurred A new pregnancy brought on an exacerbation of the osteomalacia but not of the Basedow's disease. A woman of 48 had osteomalacia for eleven years, and signs of Basedow's disease for six years Following a transitory improvement in the former, there occurred, following a serious gynecological operation, exacerbation of the osteomalacia and increase in the Basedow's disease signs Then both diseases improved.

A 45 year old woman observed by J A Hirschl (2080 and 2192) had no hereditary tendency but developed Basedow's disease in the winter of 1898 *following great anxiety* In the fall of 1899 osteomalacia pains occurred, and in January 1900 there was a distinct deformity of the skeleton associated with a shortening of the body. In May she was completely unable to walk and in September of that year a pronounced pattern of osteomalacia was recognized together with a myxedematous swelling of the

that a disorder in the functioning of the one may have, as a consequence, a disorder in the other also Revilliod (1373), who has expressed himself similarly about the relationship of Basedow's disease to osteomalacia, called attention to the phosphaturia which also occurs in Basedow attacks sometimes. He found it in 7 of 14 Basedow cases.

The first case of a combination of Basedow's disease and osteomalacia was described by v Recklinghausen (1001) Köppen's (1051) 23 year old female patient had suffered from typical Basedow's disease for five years. Later she complained of pain from pressure on the lower neck vertebrae and upper thoracic vertebra. The patient had already noticed a slight kyphoscoliosis for the past two years. At the last she complained of pains in both arms She died quite suddenly in the night, after being

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rotten wood Even in the thickest places it was very easy to cut into the *substantia compacta* The Haversian canals appeared very wide, close together and bluish red, the marrow substance was very red but it still had a fatty content Although a puerperium have never taken place, the deformity of the bones had almost the same characteristics as a puerperal osteomalacia No examination of the thyroid gland seems to have been made Koppen later saw another young woman in whom, besides the symptoms of Basedow's disease, kyphoscoliosis was present. This woman also lost most of her teeth in the course of her disease (see §208 above)

Here is added a case observed by Hoennicke (2502) It is of special interest, since it is the only one of a male The 47 year old patient from Lausitz, in Saxony, was received in the Royal Saxony Insane Asylum, of Sonnenstein, because of states of excitement and irrational illusions Up to about eight years before he had been healthy, industrious, modest and shy For four years he had developed a thickened neck and goggle eyes. Three years before admission he had developed a weakness in the feet, rheumatic pains, and had been unable to work This patient presented the picture of typical Basedow's disease; he was emaciated, and weighed only 50 kg His height was 160 cm He had a slight kyphoscoliosis and a slight case of knock-knees A noticeable increase in the curvature of the legs was not discerned in the course of the observation The patient was bedridden and weak and had fainting attacks The irregularity of the heart action increased He died nine months after admission. At autopsy it was found that the skull bones were very thin, light, soft, and easy to cut The ribs were pliable, could be broken without blows, and cut like rotten wood. The cortical layer was very thin and the marrow dark red. Even the femur could be cut through with a knife The pelvic girdle showed no conspicuous alteration of form.

Tolot and Sarvonat (2774) reported a woman of 52 who, since her youth, had had a goiter and several Basedow's disease signs She had never been pregnant A curvature of the spine led to compression symptoms of the spinal cord The examination showed tachycardia and tremor, but no distinct goiter. Soon afterward the patient died. The autopsy showed typical osteomalacia of many bones. A goiter located chiefly behind the sternum seemed to be in a "state of hypersecretion"

A case reported by Hamig (1580) belongs here also. The clinical diagnosis was only Basedow's disease This woman of 32 had an exophthalmia which remained even after death, and extremely soft bones The hyperostotic skull bones contained diploe everywhere, the inner layer was thin, slightly rough, and allowed the cutting of good sections

If we review once more the cases in which a pronounced osteomalacia is combined with Basedow's disease we find that among 13 cases on which sufficient clinical data are available, there are 10 in which the Basedow's disease preceded by a shorter or longer period. In 3 cases, 1 of Fr Mobius and 2 of Latzko, the osteomalacia was already present before the occurrence of the signs of Basedow's disease

In the great majority of the cases in which a more exact description is given the non-puerperal form of osteomalacia is involved. In one case (Hoennicke) the patient was a male Once it appeared in the puerpural form. In the case of one 48 year old woman the osteomalacia followed the last delivery and the Basedow's disease signs did not appear until one and one-half years later. (Fr. Mobius)

Other bone disorders may also occur in Basedow's disease and bear no close relation to this one as we learn from scattered observations.

Seeligmuller (531) reported a woman of 30 with a *spondilitis cervicalis* With improvement of this condition by treatment the Basedow's disease signs also improved considerably Fr Müller (1134) observed the subacute case of a woman of 25 with a kyphosis of the sixth to eighth thoracic vertebrae which developed in the course of the Basedow's disease The autopsy showed that the thoracic *sympathicus* was interrupted at the level of the vertebral caries While she was alive no special sign of this had been evident The cervical *sympathicus* seemed normal

The discovery of a bilateral disorder in the case of a female patient of 27 with Basedow's disease, described by M Bernhardt (2615) can, perhaps, be accorded a certain significance, as it is considered by some to be a sign of degeneration

Gigantism and Acromegaly

§220. In speaking of osteomalacia we were able to point out certain relationships which seem to exist between the thyroid gland and the skeletal system By experiments on animals the important influence of the thyroid gland on bone development and bone growth has been established As is known, Hofmeister, in rabbits, and V Eiselberg, in young sheep and goats, observed disturbance of growth following early removal of the thyroid glands This affected the long bones especially and consisted not only of an inhibition of the growth *in length* but also *in the thickening and rounding* out of the bones combined with a decrease in strength The ossification of the epiphyseal cartilages was delayed A retardation in growth is, to be sure, also a sign of cachexia if extirpation of the goiter has been executed in an individual still in the growing stage, this belongs among the chief indications of infantile cretinism

The observations which J Holmgren (2681) has made on a number of youthful Basedow's disease patients who were still at the age of puberty or not much older and were still in the process of growth, are of great interest not only from the clinical view point but also as an illustration of a depen-

skin of both lower legs, a firm enlargement of the thyroid gland, tachycardia, exophthalmia, the usual eye signs and tremor (see §221 below).

Before the German Medical Society in Prague v. Jaksch (2195) presented a girl of 27 who had had typical Basedow's disease for seven years In 1898 a ligation of both of the upper thyroid arteries and of the right lower one was performed Five years later a peculiar manifestation appeared in the skeletal system, starting with pain in the radius On various bones, especially the radius and ulna, thickenings appeared and *apparently spontaneous fractures occurred, followed by gradual deformation of the*

and ulna had increased Symmetrical fracturing and bending of these bones had occurred At the wrist there was now a high degree of atrophy, the shoulder blades were paper-thin, the clavicle peculiarly placed, the coracoid processes of the scapulae were distorted and the head of the humerus had separated from the diaphysis The The pelvis had assumed a typical osteomalacious form. All these changes showed distinctly in the X rays Published in 1908 (2935), the X-ray pictures show very plainly the widely opened bony cleavages, usually running all the way across In the course of time a repair by callus formation developed at all the points of separation, but even so this was not as compact as the original bone The separations, although occurring in the regions of joints, did not correspond with the physiological boundaries between epiphyses and diaphyses According to the X-ray picture it was not really a matter of spontaneous fracture but of several dehiscences of the bone tissue caused by halistereses The *bone contours themselves were very plainly visible* The P_2O_5 excretion in the urine never exceeded normal limits A pregnancy had never taken place

Dauber (2276) reports a woman of about 45 years who had Basedow's disease for *more than 10 years and osteomalacia for a somewhat shorter period* The latter did not show the characteristics of the puerperal form although the woman had given birth thirteen times

Hoennicke (2512) mentioned also that, among Hofmeister's osteomalacia material, *he had found one case of a complication with Basedow's disease.*

Revilliod (1373) found that Basedow's disease patients sometimes display an exaggerated motility of the finger joints The fingers seem overextended and the terminal joints strangely pointed He also observed an abnormal flexibility of the phalanges and striking brittleness of the bones. In the case of a woman 59 years of age, a Basedow's disease patient, there was pain in the bones, besides phosphaturia The same occurred in 2 *other cases* A woman of 38 suffered from pain in the bones and a narrowing of the fingers A woman of 62 suffered a fracture of the thigh while walking quietly

Cheadle (223) has already, in 1869, called attention to the fact that in Basedow's disease sometimes a pressure sensitivity is demonstrable over the cervical spinal column and the upper part of the thoracic column. A. Lewin (777) noted sensitivity to pain in this region under moderate pres-

... among 22 cases

If we review once more the cases in which a pronounced osteomalacia is combined with Basedow's disease we find that among 13 cases on which sufficient clinical data are available, there are 10 in which the Basedow's disease preceded by a shorter or longer period. In 3 cases, 1 of Fr. Möbius and 2 of Latzko, the osteomalacia was already present before the occurrence of the signs of Basedow's disease.

In the great majority of the cases in which a more exact description is given the non-puerperal form of osteomalacia is involved. In one case (Hoennicke) the patient was a male Once it appeared in the puerpural form. In the case of one 48 year old woman the osteomalacia followed the last delivery and the Basedow's disease signs did not appear until one and one-half years later. (Fr. Mobius.)

Other bone disorders may also occur in Basedow's disease and bear no close relation to this one as we learn from scattered observations.

Seeligmüller (531) reported a woman of 30 with a *spondilitis cervicalis* With improvement of this condition by treatment the Basedow's disease signs also improved considerably Fr Müller (1134) observed the subacute case of a woman of 25 with a kyphosis of the sixth to eighth thoracic vertebrae which developed in the course of the Basedow's disease The autopsy showed that the thoracic *sympathicus* was interrupted at the level of the vertebral caries While she was alive no special sign of this had been evident The cervical *sympathicus* seemed normal

The discovery of a bilateral disorder in the case of a female patient of 27 with Basedow's disease, described by M. Bernhardt (2615) can, perhaps, be accorded a certain significance, as it is considered by some to be a sign of degeneration

Gigantism and Acromegaly

§220. In speaking of osteomalacia we were able to point out certain relationships which seem to exist between the thyroid gland and the skeletal system. By experiments on animals the important influence of the thyroid gland on bone development and bone growth has been established As is known, Hofmeister, in rabbits, and V Eiselberg, in young sheep and goats, observed disturbance of growth following early removal of the thyroid glands This affected the long bones especially and consisted not only of an inhibition of the growth in length but also in the thickening and rounding out of the bones combined with a decrease in strength. The ossification of the epiphyseal cartilages was delayed A retardation in growth is, to be sure, also a sign of cachexia if extirpation of the goiter has been executed in an individual still in the growing stage, this belongs among the chief indications of infantile cretinism.

The observations which J. Holmgren (2681) has made on a number of youthful Basedow's disease patients who were still at the age of puberty or not much older and were still in the process of growth, are of great interest not only from the clinical view point but also as an illustration of a depen-

dence of Basedow's disease on disturbance of function in the thyroid gland. He found that nearly all were taller than the median for their ages, and in fact considerably taller than adults, and that a premature ossification of the epiphyseal cartilages could be demonstrated by X-ray. In regard to the latter observation he pointed out that, according to his experience, the epiphyseal cartilages regularly ossify earlier in individuals of especially great stature than in individuals of middle height or in the shorter ones, whether or not they have a goiter.

Among 17 Basedow patients between the ages of 13 and 20, the stature of 13 far exceeded the average and in most of these the epiphysial cartilages at the wrists were ossified except for larger or smaller remanents Thus he found, in the case of a 13 year old girl, a height of 165 cm as compared with the average of 142.2 cm, in the case of a 14 year old girl 166 cm, cf 153 5 average, in the case of a 15 year old boy 167 cm, cf 153 9 average, in the case of a 16 year old girl 167 cm, cf. 157.5; in the case of a 17 year old girl and a 17 year old boy 179 cm, cf 161 3 average, and in the case of an 18 year old girl 168 cm, cf 161 average.

R Stern (291) mentioned the unusual height of 178 cm of a female patient of fourteen years who had developed Basedow's disease at the age of 9 years, also, a youthful male Basedow patient who was conspicuously tall and possessed a massive chin.

had already made observations which belong here. He reported a fourteen and one-half year old boy who, during the first stage of Basedow's disease grew 4 cm in 10 days

In quite isolated cases a typical acromegaly is encountered in patients with Basedow's disease. In several of these cases diabetes was present at the same time, a coincidence which has been established in acromegaly several times According to Lorand (2313) the combination occurs only when it involves hyperthyroidism, but hardly ever where signs of myxedema are present In the case of the patient with diabetes combined with acromegaly, changes were found in the hypophysis, the thyroid gland, and the pancreas, especially the islands of Langerhans.

Dienot (1709) reports a case studied in 1877, at Reims, by Henrot The patient displayed the signs of acromegaly together with all the chief signs of Basedow's disease

double its normal size Lancreaux (1336) has described a similar case A woman of 40

crease in size and a rapid growth of lower jaw, lower lip, eyelids, nose, tongue, hands and feet. Murray (1625) observed acromegaly in combination with Basedow's disease in 2 cases, a woman of 37 and one of 63. Two years later he reported 3 cases of this kind. Magnus Levy (1615) stated that such a combination of the two diseases was found in an autopsied case at the State Hospital, near Urban Place, in Berlin.

R. Stern (2991) was impressed by the massive development of the chin in several of his Basedow's disease cases, although no other sign of acromegaly was evident.

Signs of Myxedema

§221. Of special interest and instruction for an understanding of the pathogenesis of Basedow's disease is the occurrence of signs of myxedema in the course of Basedow's disease. This combination can develop in various ways. In a few rather rare cases single signs occur differing from or replacing the typical signs of Basedow's disease. These belong to the pattern of myxedema. Suitable treatment may cause both symptom complexes to subside or one may disappear while the other continues.

More frequently the sequence is as follows: in the course of Basedow's disease certain of its signs regress and are replaced by those of myxedema. With a gradual remission of the former the early signs of the latter stand out more and more plainly, so that one can speak of a spontaneous transition from Basedow's disease into myxedema. The signs which persist the longest usually are tachycardia and exophthalmia.

It occurs much more rarely that in the course of a fully developed myxedema, signs of Basedow's disease develop or its complete symptom complex arises in place of the former disease.

Spencer Watson (637) was probably the first to call attention to myxedema signs in Basedow's disease before the Medical Society in London. He presented a small girl who, besides the main signs of Basedow's disease, had a striking slowness of speech and mental dullness which formerly had not been among her traits.

Kowalesky (842) observed a woman of 46 who had an inherited tendency, and who had suffered from epilepsy since her nineteenth year of life (see §118 above). She developed a cardiac palpitation in her fortieth year. In addition, the other typical signs gradually appeared. With an exacerbation of the Basedow's disease came a swelling of the legs from the ankles to the knees. The skin over this was tight, dry and cool. Finger pressure left an indentation lasting only a short time. A similar swelling developed on cheeks and lips. For a time the hands were also swollen. Then came a loss of hair from the head and axillae, and within two months eight teeth fell out. The body temperature was subnormal. In place of earlier excitability and attacks of fury she experienced a great apathy. The woman became dull of understanding and behaved as if half asleep. The facial expression was stupid, the tongue was thick and the mouth full of mucus. During this stage the main signs of Basedow's disease continued. Warm baths, quinine, arsenic and other medicaments caused the signs of myxedema to disappear spontaneously. Only those of Basedow's disease and a pronounced anemia remained.

Sollier (1005) reported a woman of 31 who had become very nervous, suffered from

agoraphobia, and had noticed, for about one year, that her eyes protruded He found conspicuous exophthalmia, definite tremor, tachycardia, reduction of electrical skin resistance, and a history of episodes of heart consciousness. The thyroid gland could hardly be palpated. Most conspicuous at first sight, aside from the exophthalmia, was a puffiness over the whole body It appeared most plainly at times of fatigue or excitement and during menstruation This edema-like swelling which was not equal on the two sides, seemed firmer on the legs than on the hands Hydropathic and electrical treatment improved the condition rapidly Exophthalmia and tremor disappeared completely The swellings returned a few times during menstruation, but only for short intervals The nervous symptoms subsided. At the end of the observation, six weeks later, improvement was continuing The second case, a 39 year old woman, had the myxedematous swellings extending over the whole body, but greater, more noticeably resistant and hard and more prominent on the legs than on the hands On [illegible]

[illegible]

in volume and slightly hardened

Stabel (1510) mentions briefly a 50 year old female patient with palpitation, a distinct Basedow's disease goiter, and signs of myxedema at the same time. Thyroid gland treatment resulted in a substantial improvement

Jeunet (1740) reports a 24 year old patient of N Faure who had a myxedematous appearance besides pronounced signs of Basedow's disease [illegible]

she perspired profusely, lost a large part of the hair from her head and, in spite of the enormous swellings on the legs, lost 28 kg within six months Since her last pregnancy, six and one-half years before, pains in the back, pelvic bones and ribs had gradually developed It became noticeable to the patient that, little by little, she was [illegible]

[illegible]

stipation, swelling of the face, especially of the eyelids, and swelling of the hands. The thyroid gland was symmetrically enlarged, distinctly pulsating, with a continu-

ous *bruit* over the lateral lobes The heart beat was forceful, the tachycardia moderate Use of ergotin resulted in improvement Although the face remained somewhat swollen, the patient resumed work. A later report, from the year 1899, seems to relate to the further course of the patient just mentioned The skin was swollen There was moderate tachycardia with a slight exophthalmia and a tendency to bloody diarrhea. Thyroid-gland therapy led to loss in weight, polyuria, glycosuria and albuminuria. Finally, maniac attacks occurred, followed by death from exhaustion

Meige and Allard (1998) observed a 28 year old patient with edema of the upper eyelids, mental dullness and attacks of drowsiness, together with the classic signs of Basedow's disease Courmont (1834) also observed the combination of Basedow's disease and myxedema in the case of a young girl

Ulrich (2028) reported that among 4 cases 2 showed concurrently the signs of both diseases A girl of 19 had exophthalmia, v Graefe's sign, v Stellwag's sign, Mobius sign, tremor of the extremities, diaphoresis, a tachycardia of 108 beats per minute, and a profound depression. The thyroid gland was not palpable, the face appeared swollen, the breast glands were undeveloped, the hair of the head was scanty and, in places, fell out The patient was slow of movement and the speech dragged Ulrich found a girl of 15, small, delicately built and shy who had a pulse rate of 108 beats per minute, a slight tremor of the extremities and of the trunk There were occasional choreiform movements There was some degree of imbecility, slow speech, lack of perspiration, and some scaling of the skin of the face The thyroid gland seemed only slightly enlarged, soft, and non-pulsating

J A Hirschl (2080 and 2192) observed the interesting case of a 45 year old woman without hereditary tendency After the death of her husband and the severe illness of one of her children, this patient developed Basedow's disease Not quite a year later she experienced osteomalacia pains and after four or more months a typical osteomalacia could be demonstrated (see §219 above) At about the same time a myxedema-like swelling occurred on the skin of both lower legs The goiter was very hard On the right it was the size of a walnut, on the left the size of a hazel nut There were also present exophthalmia, all the eye signs, tachycardia and tremor The body temperature was subnormal Hirschl (2192) also mentions another case, a 32 year old woman who, besides the typical signs of Basedow's disease, showed several signs of myxedema The skin was not moist It itched to a troublesome degree The eyelids were swollen, but free of pain A goiter of pigeon-egg size, of moderately hard consistency had no audible *bruit*

Hainaut (2078) reported a 17 year old girl who had signs of myxedema, together with palpitation, tachycardia, and exophthalmia After administration of thyroid tablets and electrical treatments the condition improved Only the rapid pulse remained.

Holub (2682) reported a case which he observed and which belongs here It is of special interest because an older sister of the patient suffered from Basedow's disease, 3 older sisters and the mother each had a goiter Three years later the eyes of this 16

exophthalmia was found together with v Graefe's sign, a moderate goiter without a *bruit*, a pulse rate of 120 and a delicate tremor Skin of cheeks and lids appeared pale and swollen There was a slight increase in the mechanical irritability of the *N facialis* Her height was 136 cm Under treatment with thyroid tablets the swelling of the face disappeared, the exophthalmia was reduced, v Graefe's sign could no longer be observed, the goiter became smaller, and the pulse rate went down to 96

The tremor ceased After nine weeks of treatment, the patient had grown 9 cm Six weeks after cessation of treatment, the patient again appeared with a swollen face The goiter also had grown larger, otherwise there were no changes

F E Batten (2458) reported a 10 year old child with a pale swollen face, quaking voice and waddling gait The personality was slow and dull. There was a considerable enlargement of the thyroid, a forceful heart action, and a pulse rate of from 118 to 140 beats per minute Exophthalmia was absent Thirteen weeks previously the child had fallen down stairs Two weeks later headaches first occurred, and gradually the

goiter, tachycardia and diaphoresis

Rehn (2009) in his valuable work on the surgical treatment of Basedow's disease reported a young man who at the onset of his illness displayed a swollen face reminiscent of myxedema, as well as a goiter, tachycardia, tremor and marked dyspnea The patient died soon after the operation

P Aschioté (2253) describes a woman of 40 who had a conspicuous brachycardia The pulse rate was only 55 beats per minute She also had goiter, exophthalmia, and the characteristic tremor, bradycardia was the only sign which reminded one of the *cachexia thyreopriva* It cannot be determined from the description whether the thyroid gland was not, at least in part, in a state of fibrous degeneration

Dyson (1957) presented before the Medical Surgical Society of Sheffield a woman whom he had under observation for 12 years The pulse rate had declined from 140 to 60, and the thyroid gland could no longer be palpated There was still some exophthalmia, although in less degree

Considerably greater is the number of those observations in which, after a more or less prolonged course of clearcut Basedow's disease the signs of myxedema become more and more prominent, while the signs of the former disease partly or wholly disappeared so that finally the myxedema signs dominated the disease pattern or replaced the Basedow signs entirely.

tient diminished Decrepitude and weakness followed and remained from then on This woman came under Hartmann's observation at the age of 36 At this time she displayed the most conspicuous signs of myxedema. Her gait was slow, her head fell somewhat forward and the abdomen protruded, as in a four or five months' pregnancy The face looked wax-like, the features immobile The cheek became swollen and reddened brightly with the least excitement The swelling was firm The skin of the face was dry and covered with fine scales. The hair on the head was thin, that of the armpits absent. There was weakness of memory and a dullness of the speech.

Nothing more could be felt of the thyroid In the discussion of the demonstration by Spencer Ward (639, see above) Ord mentioned that one of the cases of myxedema

Basedow's disease disapp-

of the eyelids and a pigmentation of the skin developed.

Corkhill (1095) observed that the symptom complex of Basedow's disease developed unusually rapidly in one of his cases and that myxedema followed after a few months. A previously healthy 32 year old woman experienced a bodily strain followed by weakness, anemia, dislike for work, weakness of memory, and nervous irritability Within 48 hours the thyroid gland developed such a large swelling that breathing became difficult. A *bruit* could be heard over the entire gland and the swelling increased with excitement or anger. The cardiac palpitation was disturbing, and the condition became steadily worse Four and a half months after the onset of the illness this woman showed the full picture of myxedema; there were hard, non-impressable swellings on the whole body, especially of the eyelids, slow speech and mental dulness. The heart rate no longer was accelerated The thyroid gland was still almost four times as large as normal, but of firmer consistency After subcutaneous injection of thyroid extract, the condition improved After two months the swellings had disappeared, the skin became normally soft and the woman again became mentally alert and active The anemia also improved and the thyroid gland decreased to half of its former volume

Joffroy and Achard (1119) observed a washerwoman who at 23 became ill with characteristic Basedow's disease signs After a time these signs improved but the weakness increased The skin began to thicken over the feet and then on the rest of the body *The speech became slow, and soon the pattern of myxedema was complete* The patient soon afterward collapsed and died

J. Putnam reported a case of a woman who at first had a vascular goiter, tachycardia and anemia, then a myxedema developed which quickly improved under treatment with sheep thyroid

H Williams (1162) *reported a 30 year old woman Five years after a complete cure* of a typical Basedow's disease, she developed the signs of myxedema, which disappeared completely after suitable treatment

Baldwin (1265) reports 4 such cases A boy of 10 from an Appennine village had been healthy up to his sixth year, then the typical pattern of Basedow's disease developed At 10 years of age he showed pronounced signs of myxedema Use of thyroid tablets soon improved this condition and continued use of the tablets, 4 a day, kept

gradually became more severe After five and one-half years the girl had recovered But from now on the pattern of a myxedema developed gradually which was fully developed after a year's time The continued use of thyroid tablets resulted in complete cure A 15 *year old girl with severe Basedow's disease was completely cured after* a period of about two years Five years later a typical myxedema developed but disappeared again with thyroid-gland medication A woman of 45 gradually developed the

plex of myxedema Her tongue became swollen, and the skin dry and leather-like in texture. There also was a reduction of skin sensitivity and a general sensation of coldness Improvement followed suitable treatment The second case was that of an 18 year old girl with pronounced Basedow's disease The disease had started eight years before, after repeated frights, and became worse after another fright in a carriage

accident During convalescence after a severe case of the measles, the disease pattern changed The signs of myxedema became more and more evident After a year's time this disease was fully developed. The treatment with thyroid extract had a very favorable effect Campbell Gowan mentioned three other similar cases about which he has no further details

Zum Busch (1391) reports an anemic girl who gradually developed the signs of Basedow's disease in her twenty-first year Only, no goiter could be discovered After four weeks of suitable treatment the patient was fairly well. A conspicuous increase in weight followed. The face and extremities became swollen and the formerly somewhat lively, excitable patient became quiet, morose, sleepy, and poor of memory Cardiac palpitation had ceased, the pulse was permanently slowed, the formerly freely perspiring skin became dry, brittle, and scaling, hair fell out freely, exophthalmia almost disappeared Under treatment with thyroid-gland tablets perspiration broke out on the third day, the pulse ran from 70 to 120 and the amount of urine increased considerably in volume From then on the signs of myxedema diminished step by step The remainder of the exophthalmia and the v Graefe's sign remained up to the close of the observation

H Smith (1506) and Eulenburg (1567) and (2491) have made similar observations

Léon Gautier (1719) reports a 25 year old female whom he had treated for fully developed Basedow's disease for four years She had been feeling fairly well until completely new symptoms appeared These included swelling of the face, drowsiness, retardation of the pulse from 120 or 140 down to 60 or 70, and dryness of the skin The formerly soft pulsating thyroid gland was now smaller and quite hard Only the sensation of palpitation and some exophthalmia continued Thyroidin seemed to work well

and during excitement 70 to 90, the patient suffered from precordial pains and shortness of breath, the face was swollen, the voice rough, the speech slow, she complained of sensations of cold There still remained some exophthalmia Thyroid treatment was here unsuccessful One year later the patient was admitted for signs of acute cardiac insufficiency Evidence of severe tricuspid insufficiency was recognized shortly before death The thyroid gland appeared reduced but not atrophic

F De Havilland Hall (1729) mentioned, in connection with Pasteur's demonstration, that a woman observed by him had suffered from Basedow's disease for twelve years and subsequently displayed myxedema signs Thyroid extract brought an improvement.

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goiter now felt hard. Moderate tachycardia, exophthalmia, and tremor continued Thyroid tablets produced an improvement at first But this was followed by heart

peared. Then came attacks of tetany and a return of the facial swelling, diarrhea, and an increasing cardiac weakness Death occurred four years after the onset The thyroid gland seemed to have turned into a firm ademona weighing 100 gm.

Imredy (1860) observed a patient who had suffered from Basedow's disease for five

years He had improved considerably at a high altitude health resort but face and neck gradually began to swell, drowsiness and a weak memory developed, and a careful examination revealed definite signs of myxedema This condition improved following the administration of thyroid tablets The size of the goiter was not reduced but the thyroid gland seemed to have undergone a change

Sittman's (1917) briefly stated case of Basedow's disease with sclerodermia in plaques, which later turned into myxedema, has already been considered (§217 above)

Guthrie (2074) presented to the Harvey Society a woman of 58 whose pronounced myxedema had followed a Basedow's disease which he himself had diagnosed a year before Only exophthalmia was absent After a two-week use of thyroid extract the signs of myxedema vanished almost entirely and the pulse rate returned to its previous condition

Ulrich (2028) reports a 45 year old woman whose case history is instructive In her thirtieth year, the development of the Basedow's disease symptom complex began

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and exophthalmia had disappeared almost entirely The skin, where it was not covered with purple spots, looked like alabaster The hair had partly fallen out, and the *nails were torn and bent The skin on trunk and extremities had scaled somewhat* Also, the patient had tachycardia of 132 beats per minute, tremor of the upper extremities, great emaciation and sweating of the upper half of the body

J A Hirschl (1976 and 2192) observed a patient who, as in Corkhill's case (see above) developed the symptom complex of Basedow's disease within a short time and ended with an unusually rapid transition into myxedema A woman of 33 without hereditary tendency had typhoid in January 1899, from which she had not fully recovered Seven months later she fell on a staircase, and although she was not hurt, she was badly frightened Following this, a typical Basedow's disease developed Within ten weeks palpitations ceased, the goiter became harder, memory became weak, and the skin on the lower legs and on the face became swollen On these areas, especially on the left lower leg, it was firm and left no imprint from finger pressure It was dry but not shiny Here and there it was scaly The small hairs were absent in most places Those parts which were not swollen felt cool to the touch The change stopped abruptly at the ankle, over the knees it was more gradual On the border of the lower jaw the swelling formed a thick cushion and was of a more doughlike consistency The goiter was firm On the right it was the size of an apple, on the left the *size of a walnut Palpitation had ceased The pulse rate was 90 to 108* per minute Exophthalmia was prominent, blinking infrequent, and there was a delicate tremor The uterus was *infantile*

N B Foster (2493) reported a 57 year old woman, formerly healthy, who in her fortieth year returned from South Africa and fell ill with Basedow's disease Subsequently she had noticed a dryness of skin and hair and dull pains in the legs The skin all over her body began to swell The memory became feeble and a great feeling of weariness developed With this cardiac palpitation had rather increased. There was an emesis several times each day, a complaint of nausea and lack of appetite. Beside a pulse rate of 100 per minute, the patient displayed the full pattern of a myxedema of moderate degree The thyroid gland could not be felt Thyroid tablets resulted only in a minor and slow improvement

Weintraud (2789) at the Twenty-third Congress for Internal Medicine in Munich reported an observation which belongs here A woman had had Basedow's disease for

about 8 years With a remission in the disease symptoms an almost complete disappearance of the thyroid gland followed gradually concurrently with the appearance of a myxedema-like swelling of the subcutaneous tissue When the patient complained of *pain in the extremities, the X-ray showed a peculiar bone resorption* processes in both ulnae, one collar bone and several metacarpal bones. Tachycardia still continued, so that it did not seem advisable to give any thyroid preparations.

Burghart (2626a) reported, to the Internal Medicine Society at Berlin, a patient who for several years had suffered from an uncomplicated Basedow's disease unmistakably followed by signs peculiar to myxedema The previously white, glistening,

a considerable goiter and exophthalmia remained After administration of iodothyrin the skin again became white and shiny, the face regained its former *expression*, the eyes their sparkle, and the former vivacity returned. Heart action was again somewhat accelerated.

Herzberger (2190) and Minkowski (2547) each mention briefly a case of Basedow's disease which turned into myxedema In Minkowski's case this problem was controlled by use of thyroid tablets, whereupon the Basedow's disease recurred.

Faust (2823) saw a case in which the Basedow's disease changed into myxedema following treatment

Murray (2213) stated that in 9 among 40 cases of Basedow's disease myxedema ap-

Simonds Goodings (2830) observed a woman who became greatly run down after eleven pregnancies in quick succession In her thirty-first year she noticed a swelling on her neck, a protrusion of the eyes, and a marked tremor She also suffered from dis-

the thyroid enlargement and exophthalmia The temperature was subnormal, the

gloomy, weak, and short of breath The pulse rate, however, was between 108 and 120 even before she began to take thyroid extract.

Morrow (1890) reports a woman of 45 After a delivery, exactly symmetrical, cir-

thyroid extract these symptoms improved; but they were followed by a goiter, tachy-
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lady who had previously been healthy Two years before and without known cause, she had developed a swelling of the eyelids and cheeks, and at first, also of the hands Apathy, poor sleep, nervous and digestive disturbances, and fatigue were trouble-

[illegible]

eyelids, and moderate sweating The thyroid gland could not be felt

Ulrich (2028) reports the case of a 46 year old woman who had typical myxedema for ten years Thyroid treatment was followed by rapid improvement, the swelling became reduced, the scaling off of the skin ceased, hair started to grow again, and stool passages again occurred spontaneously At the same time, however, the pulse rate went up to 120 beats per minute, the patient sweated violently, complained of congestion of the head, and became thin The eyes both protruded.

Kocher (2197) had seen Basedow's disease signs following a pre-existing myxedema in only one among his numerous cases An 18 year old farmworker came from a family in which, for generations, every member had a goiter, he himself had a small, hard goiter, which had been present from childhood He also had a swollen face, and slightly swollen eyelids His gait was heavy, the speech slow This patient became easily fatigued and complained of cold To cure the goiter he had long been rubbing himself with iodine When he came to Kocher the signs of Basedow's disease were present These disappeared after the excision of the left half of the goiter and the ligature of the right *art thyroidea inferior* Mild symptoms of myxedema remained

Béclère (1172) described the case of a 31 year old woman whose symptoms of Basedow's disease developed in acute form after she had taken unreasonably large amounts of sheep's thyroid gland

Finally, we have still to consider the rather rare cases in which the signs of myxedema came first, usually sooner or later after a thyroidin or iodine treatment. There was an improvement or complete disappearance of the myxedema but Basedow's disease signs or a complete Basedow's disease developed

Metabolic Disorders

§222. Disorders of metabolism are among the most constant and important signs of Basedow's disease Many cases, in spite of ample nutritive intake and good digestion, show a high degree of emaciation; however, they can be restored again quickly with improvement. Not infrequently the emaciation, combined with a feeling of general weakness (see §125 above) appears among the first signs of the developing disease It may progress to a considerable degree before the symptom complex has fully developed In many cases rapid emaciation begins suddenly, either without evident cause or because of nervous or mental influences The patient may lose several kilograms of weight within a few weeks Then emaciation ceases and the previous weight is regained This cycle can repeat itself several times Huchard (1977) spoke of just such *crises d'amaigriassement*. Passler (1362) and L. V Schrotter also mentioned such cases.

The high degree of emaciation is in striking contrast with the fullness of the neck, and the protruding eyes. *The expression of horror in the gaze*, the obvious pulsation of large arteries within the neck, the sallow pallor of the skin, the flushing of the face at the slightest excitement, as well as the unsteady movements play no small part in the sometimes really terrifying appearance of Basedow's disease patients. In severe cases such great weakness goes hand in hand with excessive emaciation that the patient cannot move about alone He may find it difficult to sit up even in bed If diarrhoea and vomiting also occur, loss of strength is dangerously increased. But even under such circumstances the patients sometimes recover rapidly. Progressive emaciation, especially if it occurs following an ample intake of calories, bodes ill for the future development Prospect of improvement or cure exists only when continued gain in weight can be shown A transitory gain in substance *sometimes takes place with the intake of more* abundant nutrition even in acute cases ending fatally (Fr Muller 1134, 1st case, 48 year old woman, Hirschlaff 1733, 21 year old woman).

H Mackenzie (2537) believed that one could distinguish the lean type and the fat

face, in 5 cases nutritional condition was fairly good, and in 3 good nutritional condition was emphasized Kocher (2197) found more or less extreme emaciation in 57 among 80 cases, *i e* 70 25% In 20 case histories, however, it is especially remarked that the muscles were well developed Emaciation was great among 28 patients (35%) and in a few of these it was extreme (see below) In 23 cases (28 75%) the nutritive condition was good or fairly satisfactory In 2 of these a well developed *panniculus*

vorable influence, through operative therapy, always was associated with a gain in weight, mainly a gain in adipose tissue Among Murray's (2213) 180 cases a variable decrease of weight was recognized in 67 G Dock (2641) observed a more or less severe emaciation in all of his 32 cases Among 50 cases of Basedow's disease reported by K. Schultze (2749) emaciation was especially noticeable in 15 A wretched looking woman of 42, when first seen, hardly weighed 35 kg A gastric crisis had caused a loss of 11 kg within 4 weeks

In exceptional cases the emaciation affects only a part of the body, or is distributed unevenly.

In the first description of the disease v. Basedow (15) had emphasized this manifestation. Arms, neck, chest and mammary glands were emaciated, while abdominal region and legs were unusually full and thick (see §214 above). After repeated fluctuations and a lasting improvement, neck, upper body, chest, and arms appeared full and sufficiently nourished. The swelling of trunk and feet still remained. Quite similar cases have been described by P. J. Möbius (993 and 994) in a 59 year old woman, and L. v. Schrötter (2344) in a 27 year old woman.

Most remarkable is Chvostek's (269) fifteenth observation of a 55 year old woman. There was enlargement of the right lobe of the thyroid gland and a slight exophthalmia of the right eye, a hyperidrosis confined to the right side, and reddening of the skin. Emaciation seemed strikingly greater on the whole right half of the body than on the left. It began on the upper parts and reached the lower parts only later, when the state of nutrition of the upper part had already improved somewhat. The general condition seemed serious, but the patient recovered entirely in the course of a year.

The case reported by G. F. Johnston (1120) was a 45 year old man. Excessive emaciation with muscular atrophy was more evident on the right than on the left. A tremor affecting the entire body was stronger on the right. Only the right lobe of the thyroid gland was enlarged.

Examples of a rapid decrease of body weight in the course of Basedow's disease are plentiful in pertinent literature.

Chvostek (399) observed a man of 46 who illustrated this rapidly progressing emaciation. The body weight including clothing, overcoat, and hat was only 40 kg. J. Russell's (567) patient, 32, had diarrhea and vomiting and an occasional voracious appetite. He lost 30 kg within a year. During a stay in the country he gained back 6 kg which he lost again as soon as he was back in the city. Isaac (981) reports a patient whose weight changed from 107 to 76 kg. Emaciation was a constant sign in the 5 cases which Fr. Muller (1134) described up to their death. It accompanied great debility and weakness. The patients were bedridden all of the time. In the later stages they were unable to raise themselves. A woman of 48 who, before the illness, had been well nourished, lost 8 kg in 7 weeks. A woman of 36 lost 16½ kg in 4 weeks, a 25 year old woman lost 20 kg in 9 months through a subsequently discovered digestive disturbance. The latter patient, 9 days before death, weighed only 32 kg. Also, among 47 case histories reported by Mannheim (1222) there are several significant examples of rapid emaciation. A woman of 43 lost 20 kg in one year, a woman of 35 lost 2 kg in eight days. A woman of 32 who before the onset of the disease weighed 93¼ kg had severe palpitations after a violent fright, and began to become emaciated rapidly. Two months later diarrhea occurred, and now, for the first time, the other signs of Basedow's disease developed in number. This patient had diarrhea, vomiting, and polyphagia, especially at night. After ten months she had lost about half of her former weight. Clinical treatment definitely improved her condition but repeated and severe relapses occurred. Pfibram (1368) mentioned that one woman lost 20 kg within a short time. Revillard (1373) reported the fatal case of a 64 year old woman who lost 60½ kg. Gruneféld's (1445) female patient of 33 had a relapse and lost 10 kg in a short time. Bonnet (1695) reported a man (11th observation) who, after a violent emotional excitement, developed Basedow's disease and polyuria, and became so emaciated that he declined from 102 kg to 62 kg. A woman of 48 with severe Basedow's disease combined with myxedema and osteomalacia, as reported by Fr. Möbius, (1885), became so thin within six months that, in spite of enormous edema of the legs, she lost 28 kg. Arneill's (1934) 33 year old patient with acute Basedow's disease lost

35 kg in four months Brener (1944) observed a woman of 27 who lost almost 10 kg in two weeks Herbet (1973) reported Jaboulay's patient who had lost 25 kg within a year J A Hirschl (2192) reported a loss of 39 kg in the case of a 34 year old man with severe rapidly progressive Basedow's disease Hirschl (2383), two years later, presented before the *Verein fur Psychiatrie und Neurology* in Vienna, a 36 year old Basedow patient with a deep bronze coloration of the skin. Extreme emaciation was a conspicuous sign In 100 days he developed a high grade motor weakness (by measure on the dynamometer left 16 kg, right 14 kg) and increased excitability. Runge (2228) reported 2 of his cases from the Gottingen clinic. Within a short period a loss of 15 kg and of 25 kg respectively was registered One of Kocher's numerous cases (2197), a woman of 31 lost 40 kg in three months during a rather acute phase of the disease Lanz (2306) reports that the loss of weight amounted to 15 kg in one and 24 kg in another severe case, both within a short time One of Murray's (2553) patients weighed 43 kg at the height of the disease and 69 kg after a complete cure All of the 4 accurately described female cases of K Alt (2602) showed gradual emaciation There was one woman of 53, 165 cm tall who weighed only 34 kg and was emaciated so that she resembled a skeleton Edema was present on both legs, in the knee and ankle regions Incipient edema was apparent in the sacral regions

Passler (1362) saw, in 14 among his 51 polyclinic cases, rapid loss of weight in spite of ample diet, the loss often alternating with periods of rapid gain

§223. Although it has always been recognized that a more or less severe emaciation is a characteristic sign of Basedow's disease, attention has been directed only recently to the metabolic disorders and the nature of these disorders Fr Muller (1135) deserves gratidude for being the first to have conducted exact metabolic investigations of Basedow's disease along strictly scientific lines

In the case of a 25 year old woman with severe Basedow's disease, fatal in ten months, he determined, during a five day experiment, the caloric value of the weighed food and the total nitrogen which was excreted in urine and feces, as well as the sodium chloride and phosphoric acid in the urine Weight was recorded by scales during the period of experiment. However, it must not be overlooked in the determination of the protein balance that in this disease, the skin also, in addition to the kidneys and the intestine, secretes a not inconsiderable amount of nitrogen which can be determined only approximately A patient with severe, acute Basedow's disease reported by Hirschlaff (1733), had a daily excretion through the skin reckoned as several grams.

Under normal conditions a diet of 45 calories per kilo of body weight and 24 hours of rest is sufficient to maintain the nitrogen balance Emaciated patients during convalescence may in fact retain nitrogen on this intake However, the Basedow patient of Fr Muller failed to gain on a diet of 58.2 calories per kilo and a protein intake of about 68 grams, in spite of good assimilation of the food through the intestine

Several years earlier Lustig (917), under v. Leube's direction, investigated 2 patients with Basedow's disease, a 15 year old girl and a 32 year old servant girl Each

had a moderately severe form of the disease but was of healthy appearance A healthy-

[illegible]

patients, the 15 year old girl who had the severest disease, an increase in the decomposition processes was evident, as the urea output always far exceeded the NaCl output

Later investigators confirmed the fact that, regardless of sufficient caloric and protein intake among patients with Basedow's disease, a nitrogen deficit can often be shown, especially in severe cases. Perhaps a nitrogen balance can be reached by very high protein and caloric intake Especially in chronic cases periods of great loss of protein alternate with those of undisturbed protein assimilation. Spontaneous or other improvement may effect a considerable retention of protein

A. Steyrer (2885a) has, at the suggestion of Fr Kraus, carried out metabolic investigations of longer duration, with complete metabolic and energy equilibrium studies while taking careful precautions against error. He used Pettenkoffer's apparatus The experiments showed a significant increase in the total caloric output. The increase applied to the protein balance as well as to that of the fats Under the same nutritional and environmental conditions, conspicuous variations in caloric output occurred parallel with the variations in the general nervous excitability of the patient Rudinger (2970) showed from his investigations of the protein balance of two Basedow's disease patients that some nitrogen loss takes place if an almost nitrogen-free diet is given However, with a continued diet of more than normal carbohydrates and fat, it is still possible to reach the Laudergreen minimal nitrogen limit, that is reduction of the nitrogen excretion to that amount which is absolutely essential to the maintenance of the life functions of organisms.

Magnus Levy (1344) and Stuve (1515), at v. Noorden's suggestion, extended these investigations by determining the N_2 balance, O_2 consumption and the carbon dioxide output Using as a basis the results of Zuntz and Geppert, they calculated the respiratory quotient in Basedow's disease patients and compared these values with the values for normal persons. While the normal values agree entirely with those obtained under generally similar conditions, it became evident that all the Basedow's disease patients studied had a considerable increase in gas exchange

In 2 healthy control persons, a woman of 30 and a male of 23, weighing 49 kg and 58 kg, respectively, Magnus Levy found the O_2 consumption per kilo and minute to be an average of 3 86 cc per min The CO_2 output was 3 19 cc per min and the respiratory quotient 0 85. On the other hand, in the case of a 21 year old female with Basedow's disease weighing 49 kg, the O_2 consumption per kilo per minute was 4 28 cc per min The CO_2 output was 3.36 cc per min and the respiratory quotient 0 78 In the case of a 25 year old man weighing 50 kg the O_2 consumption was 6 43 cc per

min., the CO_2 output was 4 84 cc per min., the respiratory quotient was 0 75, in the case of a 20 year old man of 55 kg the O_2 consumption was 5 24 cc. per min., the CO_2 output was 4 06 and the respiratory quotient was 0 78.

In 1897 Magnus Levy (1615) reported similar studies on 13 Basedow's disease patients, including 10 with a severe form of the disease, and 3 with a mild form Of the 10, 9 showed a considerable rise in interchange of gases in comparison with healthy people of about the same weight. In the 3 only slightly ill cases the interchange of gases, with a medium or good diet, was about the same as in the healthy persons

These ratios are elucidated very clearly in a table published in 1906 (3709) which I am reproducing here.

	Age in years	Height in cm	Weight in kg	O_2 ccm	CO_2 ccm	O_2 ccm per kg	% of normal value
1 Acute, very severe case	20	158	50 7	384 9	295 0	6 89	170
2 Very severe chronic case	26	150	50 5	344 0	236 2	6 80	170
3 Severe chronic case	22	161	55 1	305 8	256 0	5 55	142
4 Somewhat milder chronic case	50	156	43 0	266 9	219 3	5 31	122
5 Mild case	20	148	45	213 2	181 1	4 74	105
6 Cured by operation 10 years ago	40	171	84	282 8	241 0	3 37	100
7 Simple goiter	36	162	51 5	176 7	134 1	3 43	90

The basal metabolism determined by measuring the gas exchange in the lowest state, when comfortably lying on the back, and avoiding all bodily movement, rises in severe Basedow's disease as much as from 30 to 50 or even to 70 and more percent above the normal It cannot be attributed to an increase in muscular activity, as, for instance, tremor or general bodily unrest, or to the increased respiratory and heart activity. Long-continued deviations of such a degree occur in no other pathological state

During remission of the disease, or with permanent improvement, the O_2 consumption declines concurrently with a reduction in nitrogen loss and the beginning of a positive nutritional balance and it can nearly or completely approach normal values.

We have seen that conspicuous emaciation occurs, often right at the beginning of the disease. Even before this emaciation has reached full development, a pronounced increase of the respiratory exchange can be determined very early corresponding to it. Therefore, increase in O_2 consumption presents a characteristic which can be of importance for the diagnosis of incompletely developed cases.

H Salomon (2432) reports such a case, a 25 year old seamstress *She* had a moderate goiter and a pulse easily accelerated to 90, 100, and more There was a fine tremor Eye signs were absent Other disturbances were not evident, but the determination of the oxygen exchange showed a *considerable* increase of O_2 consumption, 5 9 cc per kilo per minute (*respiratory quotient* 0 735)

From wha[illegible] been said it is self-evident that a *determination* of the respiratory [illegible] for the prognosis

Salomon [illegible] 40 had Basedow's disease ten years [illegible] the neck remained For the final four months nervousness [illegible] had become evident There was *some irregularity* of the heart and a pulse of *100 to* 120 beats per *minute* Except for a slight swelling of *the lateral* lobes of the thyroid *no* Basedow's *disease signs appeared* The urine contained small *amounts* of sugar and acetone Two respiratory tests on the patient *showed an* O_2 consumption of 7 3 *to* 7 0 cc/min per kilo and a respiratory quotient of 0 744–0 706 *It cannot* be determined whether during the long interval almost without symptoms, the gas exchange characteristic of Basedow's disease was *in effect* or whether it had flared up recently *Nevertheless, the discovery* of the *great* acceleration of the oxidation process in this case makes the prognosis much *more serious* Five months later death followed temporary recovery

E Přibram and O Porges (2963) carried on experiments with basal metabolism in Ba*sedow's disease* under the influence *of high protein* and low protein *diets.* These studies demonstrated a parallel between weight and the kind of diet in the sense *that* the diet correct in nitrogen and meat *led to negative nitrogen* balance, reduction *of body weight*, *and* deterioration of *the* general condition notwithstanding a large caloric intake *An* analogous effect in the form *of an* increased utilization *with* overfeeding *of protein* made still more evident the significance of the respiratory gas exchange In the *nitrogen-free* intervals of a series *of* experiments, the amount of ex*creted* O_2 was 5 9 to 6 cc/min average per kg of body weight, in the protein feeding periods *it* was 6.3 to 6 57 cc/min The above investigators added *that* a *protein or meat diet with low carbohydrate* content results in an increase in basal metabolism *not only* among patients with Basedow's *disease* but to a certain extent among normal persons also The excretion of *sodium* chloride *in the* urine was, in most *of the* cases in which it was taken into consideration, *in proportion* to the volume of the urine

The volume of phosphoric acid in the excreted *urine* has often been absolutely *increased* in Basedow's disease Since *a considerable* and variable amount of phosphates also leaves the body through the intestine, these as well as the volume of P_2O_5 taken in the food, must be determined at the same time if definite conclusions *concerning* the metabolism are to be drawn from the P_2O_5 content of the urine (see also below)

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tion. (See §226 below.) Therefore, the multiple retinal hemorrhages often observed in other severe cachexias, have, to my knowledge, never been found in Basedow's disease, a fact to which L. Pick (2112) has already called attention. While there is almost always a lack of appetite in fever and cancer cachexias, *in Basedow's disease we find very frequently an abnormally increased desire for food*.

The conspicuous *variations not only in protein balance but also in total* oxidation are peculiar to the metabolic processes and the emaciation of Basedow's disease to which we have often called attention.

Scholz (1377) could show during his experiments, even from day to day, in almost regular succession, a conspicuous rise and fall in the nitrogen excretion. Similar variations were also evident in the metabolism experiments of Steyrer (2885a) (see above). Very definite daily variations in nitrogen excretion were observed by Rudinger (2575) in 2 Basedow's disease patients. The graphs accompanying his report show this fluctuation of the nitrogen value. The phosphoric acid excretion in the urine showed similar variations, which, however, did not run parallel to the nitrogen fluctuations. An increase in P_2O_5 excretion corresponded to a low N value. P. Clemens (2633) could not find any such fluctuations of nitrogen excretion, but he did find great differences in nitrogen excretion during the course of the disease.

These fluctuations *sometimes seemed to have a distinct relationship to the nervous and mental symptoms of Basedow's disease* (see Steyrer above). When these, especially the latter, deteriorate, sometimes a considerable increase in emaciation sets in, which, with improvement of the nervous symptoms, just as quickly gives way to an increase in weight.

Such observations led Fr. Müller (1134) to the assumption that the metabolic processes in Basedow's disease might be dependent upon changes in the nervous system. Under normal conditions the most important regulator for a proper state of nutrition is the appetite. It increases when greater demands are made upon the body and decreases during bodily and mental rest. *Mental influences show their effect on the nutritive state of the body probably, in the main, through the agency of appetite.* The appetite is reduced during anxiety and by depressing experiences and increased by pleasant reactions. In Basedow's disease, however, deterioration of the nutritional state can very frequently be observed notwithstanding a normal or abnormally increased appetite and an almost normal absorption through the intestinal canal. With an intake of more than sufficient calories in relation to the usually low weight it still becomes inadequate. We know that, under normal conditions and all external circumstances being equal, there is a marked constancy in the volume of gas exchange in each individual. *But in Basedow's disease we often find, even under apparently constant external conditions, significant fluctuations in the respiratory gas exchange.* Human caloric requirement is very different according to whether the in-

Baduel, Daddi and Marchetti (2358) found a case of Basedow's disease in which the P_2O_5 excretion from intestines was greatly increased, "a veritable phosphoric acid diabetes"

Revilliod (1373) has determined an increased P_2O_5 content in the urine in 7 cases among 14 In one patient the phosphaturia occurred spasmodically (see also §219 above)

The disturbance of metabolism in Basedow's disease is therefore, as expressed in general terms, an increase of the protein turnover as well as of the entire oxidation processes. The increase in the nitrogen exchange is, however, in many cases of Basedow's disease not very significant. Sometimes, it is not even demonstrable at all. Increase in nitrogen loss is never absent in severe cases with symptoms of cachexia. But even in these cases increased loss of protein may sometimes be prevented by abundant feeding

gen exchange was definitely increased in only 4 cases The resorption of proteins proved to be normal, that of fats reduced

A 29 year old female Basedow's disease patient from the medical clinic at Gratz, upon whom Scholz (1377) made a completely successful experiment lasting four days, showed an almost entirely normal assimilation of nutrients and a calory increase of scarcely 47 per kilo, retention of nitrogen, the weight actually increased.

Matthes (1619) in Jena demonstrated a considerable retention of protein in two experiments on metabolism performed under exactly the same conditions as before (cf also Magnus Levy's case No 6 above) In the case of a woman weighing 60 kilo, 12 9 gm of nitrogen and 40 calories as intake failed to maintain the nitrogen balance, considerable loss of protein could not be prevented Significant general improvement occurred soon after a partial thyroidectomy

P Clemens (2633) did not set up a complete metabolic-balance study but took into consideration only the volume of urine, urea, chloride, and phosphoric acid in the urine, and the weight His experiments indicated that the absolute nitrogen excretion in the urine is usually considerably increased, that an increase in protein turnover does not occur in all of the well-developed cases of Basedow's disease and that where they do occur they are always transitory.

The results presented so far seem to indicate, as Fr Muller (1624) also admits, that in Basedow's disease the increase in the total oxidation processes is primary and that of proteins is the consequence of it. It must be regarded as a very important criterion of metabolism and emaciation in Basedow's diaease, that in contrast to fever, cancer cachexia, and to other disease associated with severe cachexia, the increase in the carbon exchange is much greater than that of the protein breakdown and that the emaciation affects, in the main, the fatty tissues.

Therefore, patients with this disease as a rule are not hydraemic. The blood usually shows only slight changes, or none, in its chemical composi-

of protein loss and a retention of nitrogen De la Camp (2518a) contradicted a generalization of these results. Although he found in his experiments on Basedow's disease patients a reduction of metabolism under the influence of X ray radiation he became convinced that such a reduction also occurred in his patients quite spontaneously E Pribram and Porges (2963) did not succeed in reducing the increased basal metabolism of the experimental subjects by X-ray, notwithstanding an increase of weight.

In myxedema the metabolism remains more or less noticeably above normal. In the case of a myxedema patient weighing 42 5 kg, Magnus Levy (1467 and 1468) determined an O_2 consumption per kg of 2 88 ccm per minute (53% of normal) After administration of thyroid gland it rose to 5 49 cc/min, i.e., to a degree which the investigator had found in patients with Basedow's disease (see above) Steyrer (2285a) has obtained analogous results in metabolism experiments on a myxedema patient The nitrogen exchange was conspicuously small After administration of thyroid substance the calorie production went astonishingly high, while protein calories were reduced even further.

Among normal people metabolism rises after thyroid substance is ingested but, as a rule, not very much, and to various degrees according to the peculiarities of the individual and the amount administered Both albumen exchange and fat substitution also rise somewhat

Scholz (1377) pointed out that nitrogen excretion becomes only slightly increased among healthy individuals On the other hand, he found a significant increase of phosphoric acid excretion in the feces K Kotte (1461) undertook metabolism experiments upon himself following ingestion of thyroid gland substance He found that the average of urine volume and the N and P_2O_5 excretion in the urine had increased In a metabolism experiment carried on by Ewald (1304) on a 49 year old male the first 8 days of the experiment resulted in a small reduction in nitrogen excretion of 1 3 gm with a loss in weight of 0 2 kg, but during the following seven days, in which 11 5 gm of thyroidine was administered, the N excretion was not altered significantly On the average it amounted to a negative balance of 1 8 gm but the weight declined by 1 4 kg, only to rise again upon discontinuance of the medication This shows that the loss in weight was due chiefly to loss of body fat We have encountered an analogous behavior in Basedow's disease as a characteristic distinguishing it from other cachexias

In healthy and in obese persons, and in those with goiter, etc, long continued use of thyroid gland substance, as Magnus Levy (2709) recently stated on the evidence of experiments with Zunz-Geppert's respiration apparatus, sometimes, but by no means always, results in a rise of the basal metabolism

This becomes evident usually only after several weeks and remains within moderate limits Even in Basedow's disease patients the intake of thyroid substance does not necessarily call forth a rise in the oxidation processes if it is a mild case and the patient is in good condition otherwise The oxidation

dividual is at absolute rest or is active or doing heavy work. Magnus Levy (1615) correctly pointed out that people doing heavy work certainly have a greater daily assimilation than the severest case of Basedow's disease with a tremor which is continuous even during rest, and with all their general restlessness But while the healthy organism easily compensates the physiological increase of his metabolism by means of increased appetite, it is not the case with the abnormal elevation of metabolism of Basedow's disease patients for long periods, in spite of avid appetite and undisturbed absorption of nourishment

All experience collected so far on the nature of the metabolic disturbances in Basedow's disease compel the assumption that the cause of the abnormally increased metabolism, as well as the inability to replace used material, is of a toxogenic nature That this poisonous action must differ from that, for example, in cancer cachexia or in fever, follows from the peculiarities of the metabolic disturbances in Basedow's disease which we have outlined in detail above Here, one may hardly assume that the increased carbohydrate exchange is caused by direct chemical-toxic action on the fatty tissue I would much rather support the expressed assumption of Fr. Kraus (2696, p 51) that the acceleration of the oxidation process is produced by stimulation of the center of heat regulation This can, however, quite well be of toxogenic origin (see §225 below).

If it must be assumed as very probable that the *glandula thyroidea* even under normal conditions is to be counted among the organs which regulate metabolism, it can hardly be doubted that the thyroid plays a very important part in the peculiar alterations of metabolism in Basedow's disease.

This may be concluded not only from the action of ingested thyroid substance on healthy or diseased individuals but also from the evidence that a close relationship exists between increased metabolism and the diseased thyroid gland Matthes (1619) determined that, after partial removal of a goiter, the previously considerable protein loss fell to 25% of its former value When he had the excised portion of the goiter dried, pulverized and ingested, the *N* excretion again rose immediately, though not to the degree it had reached before.

The question as to whether every goiter extirpation is followed by a reduction of nitrogen loss Matthes could not conclude definitely because of various accidents But he thought it not very probable that patients with ordinary goiter who had been able to keep their nitrogen balance with small amounts of protein should perceptibly decrease their protein retention after this procedure Magnus Levy (1615) also stated: "goiter alone produces no increase of gas exchange" (see table No 7)

Rudinger (2875), by his metabolism experiments on Basedow's disease patients whose goiters were subjected to X-ray radiation found that the result was a reduction

of protein loss and a retention of nitrogen. De la Camp (2518a) contradicted a generalization of these results. Although he found in his experiments on Basedow's disease patients a reduction of metabolism under the influence of X-ray radiation he became convinced that such a reduction also occurred *in his patients quite spontaneously* E Pribram and Porges (2963) did not succeed in reducing the increased basal metabolism of the experimental subjects by X-ray, notwithstanding an increase of weight

In myxedema the metabolism remains more or less noticeably above normal In the case of a myxedema patient weighing 42.5 kg, Magnus Levy (1467 and 1468) determined an O_2 consumption per kg of 2.88 cm per minute (*53% of normal*) *After administration of thyroid gland it rose to 5.49* cc/min, *i e.*, to a degree which the investigator had found in patients with Basedow's disease (see above). Steyrer (2285a) has obtained analogous results in metabolism experiments on a myxedema patient. The nitrogen exchange was conspicuously small. After administration of thyroid substance the caloric production went astonishingly high, while protein calories were reduced even further.

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increase following the administration of thyroid substance occurs in full only in persons who lack the thyroid gland, in cases of myxedema, and in those with a thyroid-deficiency cachexia. Steyrer also (2885a) found in his Basedow's disease patients that the administration of thyroid substance even in large doses did not call forth a noticeable rise in the energy consumption.

On the basis of earlier experiments of Magnus Levy (1467) on obese subjects with the administration of thyroid tablets when O_2 consumption and CO_2 excretion as well as the total of oxidation processes went way up, C. V. Noorden believed he could point out that the administration of thyroid substance offers a means of producing a considerable increase in the oxidation processes of organisms, independent of muscular activity.

The numerous metabolism experiments performed on dogs which were fed thyroid-gland preparations consistently demonstrated a rise in the decomposition processes.

Georgiewsky (1575) proved that for dogs which were in nitrogen balance, the excretion of N and P_2O_5 was significantly increased in the urine by administration of thyroid substance Chloride content of the excreted urine was also increased. The assimilation of N from the food underwent no change as long as no manifestations on the part of the stomach and intestine occurred The animals were finally quite emaciated There was a marked loss of fat and of skeletal muscle Ross (1644) found a considerable increase in the excretion of N, NaCl and P_2O_5 by a dog during a period of feeding with thyroid gland Fr Voit (1675) has studied the entire metabolism in dogs during the more prolonged action of thyroid-gland preparations. He determined the nitrogen excretion in urine and feces and the respiratory gas exchange during abundant feeding of meat and fat The protein balance as well as the carbon dioxide production were found to be considerably increased In spite of plentiful addition of fat to the diet it was not possible to make the body retain its normal content

Taking into consideration the fact that questions of metabolic physiology can only be answered accurately after a long-continued series of experiments, in human beings such metabolism experiments, which demand a uniformity of diet over a long period, meet with difficulties Schondorf (1675), at the suggestion of E Pfluger, undertook such experiments on the influence of the thyroid gland upon the metabolism, especially that of protein metabolism A dog was fed uniformly for months after he had been brought into metabolic balance and nitrogen balance The experiment lasted nine months The object in view, that of giving the dog a daily diet of exactly the same weight in calories, was attained in a manner quite sufficient for the purpose of the experiment These very carefully executed investigations showed that when the dog was fed with thyroid gland in a continuously uniform diet 1 the already known result was a considerable increase in the metabolism 2 the thyroid gland diet had, at first, no influence on the albumen exchange, since the initial rise in *N* excretion was merely the result of the increased excretion of urine and other *N* containing extractive matter 3. As the increase in oxygen consumption with simultaneous loss of weight became evident, the increased demand was compensated by the use of the body fat. 4 Only after the fat content had declined to a certain minimum was the protein also affected 5 After cessation of the thyroid diet the rise of metabolism declined again and weight increased by accumulation of fat and protein

An experiment described by Fr Kraus (2697) shows that the thyroid material requires a long time for its action. One or two feedings, even of large amounts of iodothyroglobulin may not significantly alter the nitrogen exchange of a dog The metabolic balance for the preceding period showed a positive nitrogen balance of 0 53 gm, and during these two days a minus balance of 0 36 gm

The investigations of Eppinger, Falta and Rudinger (2922) demonstrated that the rise in protein turnover resulting from artificial hyperthyroidism in dogs can be reduced to normal by the administration of carbohydrates The thyroid gland therefore also controls that part of the protein balance which can be reduced by carbohydrate, that is, which lies above the minimal nitrogen limit of Landergreen

The protein sparing action of carbohydrate is explained by these investigators, on the basis of their experiments, by the interaction of glands of internal secretion The pancreas and thyroid glands stand in a mutually inhibiting relationship to one another, overactivity of the pancreas creates a relative restraint on thyroid activity and vice versa If, as they assumed, an abundant carbohydrate diet acts as a stimulus on the pancreas, a reduction of thyroid gland function may be expected which would find its expression in the protection of protein from oxidation In conditions of hyperthyroidism, in which an increased function of the thyroid gland exists independently, protein feeding, especially when continued over a long period, and, especially, with restriction of carbohydrate would reduce the activity of the pancreas with theoretically favorable results This actually applies, as we have seen above, to patients suffering from Basedow's disease The case of Hirschlaff (1733), mentioned several times, shows clearly that, with an unusually large portion of protein by forced alimentation, no favorable influence upon the disease was attained notwithstanding a gain of weight, and death could not be postponed

The experiments with thyroid in the diet also resulted in the recognition of the not unimportant fact that phosphoric acid excretion in urine and feces increases It appears, therefore, that the thyroid gland is also of importance for the phosphoric acid exchange and for the exchange of organic substances containing P_2O_5, lecithins, nucleins, and of protagons.

Falta (3033), in conjunction with other investigators, has found that thryoid gland acts as a stimulant to the turnover of salts. The salts of phosphorus, sodium and calcium are excreted in large amounts by the intestine

I would like to point out here also that Alb Kocher (2197) has carried out a series of carefully performed experiments, partly under Kefter's guidance, dealing with the iodine and phosphorus content of normal and of goitrously diseased thyroid glands A striking mutual relationship exists between the iodine and the phosphorus contents, so that when the phosphorus content decreases the iodine content decreases and vice versa In Basedow's disease goiters he found that with the decrease of iodine content already shown by others, the phosphorus content can rise to double This relationship is less evident in the initial stages of Basedow's disease A Kocher demonstrated in animals that when phosphorus was withdrawn from the diet the phosphorus content of the thyroid gland was reduced to half Following administration of thyroid tablets the phosphorus content decreased simultaneously with the increase of the iodine content, even when phosphorus was administered Oswald (2216) has modified these results in his report that an increased phosphorus content

is found only in colloid-poor goiters, here, the increase in volume is chiefly the result of multiplication of the cellular elements, thus, the content has increased in nuclein This, as we shall see, applies exactly to the goiters of Basedow's disease The phosphorus content, as A Kocher also discovered, is actually *less when secondary degeneration* by proliferation of connective tissue has occurred.

Urobilinuria is also encountered in Basedow's disease It appears whenever hemoglobin has been destroyed

§224. French investigators believed that the hypothetical poisons, which they thought were contained in the blood of patients with Basedow's disease, were transmitted to the urine, and would be found there either in unaltered form or modified in various ways. In order to test this theory they used a method worked out by Bouchard[1] This investigator believed that he had proved experimentally that a healthy person produces, per kilo body weight in 24 hours, a nearly constant amount of urine poison—urotoxin. This is his designation for the amount of urine which, for each kg of body weight, proves fatal when injected into the veins of an experimental animal. In this way the toxicity of the urine was tested under various pathological conditions Chevalier (882) made a number of intravenous injections in rabbits of urine from Basedow's disease The toxicity of urine neutralized by carbon dioxide was notably greater than that of normal urine, and it varied during the various phases of the disease For example, he cites a case in which urine from a young female Basedow's disease patient free from sugar and albumen, was injected into a vein in the ear of a rabbit The result was a lowering of body temperature of the experimental animal to 36° C The pupils became very narrow, the animal displayed general weakness, became unresponsive, and died the following night

Boinet and Silbert (1023) who concentrated the urine of patients with Basedow's disease by boiling it, obtained two series of ptomaines, one by treatment with caustic soda and the other by treatment with oxalic acid. A ptomaine obtained in the first series, isolated by means of alcohol, produced spasms with slowing and weakening of heart action and final cessation during diastole Another, obtained with benzine, caused intensive spasms, with less effect upon the heart. A third ptomaine extracted by the use of ether resulted first in intensified muscular irritability and then arrest of the heart during systole. Of the second series of ptomaines, the one obtained by the use of alcohol produced a motor paralysis with reduction of temperature and, after a temporary rise, weakness of the cardiac contraction, and arrest of the heart during diastole. The preparation obtained by use of ether produced convulsive movements and arrest of the heart during systole

Regolo (2117) also has tested the toxicity of the urine of a 24 year old

Basedow's disease patient according to Bouchard's method He found considerably increased toxicity Caro (2812) collected 10 cc of urine with sterile precautions from a 38 year old patient with rather severe Basedow's disease. He injected this into the abdominal cavity of a guinea pig The urine contained urobilin, acetone and acetic acid but no sugar. The guinea pig remained healthy. However, two days later, after two-thirds of the goiter of the patient had been excised and symptoms of severe poisoning had appeared (temperature rise to 40°, pulse of 180, great nervous unrest, dulled sensory state) 10 cc of urine taken from the patient with all precautions, were injected into the abdominal cavity of a guinea pig. The animal died the same night with symptoms of poisoning

It seems to me that we must look upon these experiments still with great reservation and consider that they are in no way suited to permit a conclusion concerning chemical products of metabolism which are excreted Especially, it must not be overlooked that some of the toxic action of normal urine is probably not attributable to chemical bodies but that it results from the difference in osmotic pressure between the injected urine and the blood of the experimental animal The higher the former, the more poisonous the action will be Only after determining exactly how much of the action in each separate case is due to the difference of isotony between the two fluids, would it be feasible to investigate the action of chemical poisons. It remains to be seen whether this action will prove to be something which applies specifically to Basedow's disease

Hyperthermia

§225. In a preceding paragraph we have discussed the abnormal, subjective heat sensation about which so many Basedow's disease patients complain (see §165) We also have considered (§163) the frequently observed reddening of the face and the increased warmth perceptible by touch Actually, the temperature in Basedow's disease is usually at the highest normal limit and in not a few cases an increase of body temperature can be verified by thermometer No local cause such as inflammation in any organ can be discovered That the data concerning temperature rise in Basedow's disease are relatively few is due, perhaps, to the fact that temperature recordings were not regularly taken of the majority of Basedow's disease cases, especially of ambulatory cases A temporary, moderate rise in temperature can, therefore, easily escape observation.

The rise of body temperature in Basedow's disease is characterized by irregularity and instability Usually it occurs without apparent cause; sometimes emotional excitement seems to be the occasion Usually it lasts only a few days, or even only a few hours to return to normal without any

other essential alteration in the disease pattern. In more infrequent cases it can last longer to a variable degree or it can appear intermittently.

Da Costa's (2162) 32 year old female patient, had a temperature rise up to 38° every few days, without apparent cause At the same time she perspired profusely. Following that the temperature declined to normal again

It seems to be by no means proven that Basedow's disease patients in an active phase of the disease always have a temperature of about 1° above that of healthy persons, as stated by J. Jacob (2687).

If any rise in temperature occurs it usually remains moderate. Usually it does not go above 38 or 38.5 degrees C. Only in severe acute cases, in which a temperature rise is rarely entirely absent during the course of the disease, it sometimes suddenly reaches a significant 39° or even 41°, especially before death At the same time the pulse rate usually increases, dispnoea occurs, and sometimes there is delirium (see §159 above). More *rarely a temperature rise is discernible at the very beginning of the illness.*

A 30 year old servant girl, previously in glowing health, was described by Friedreich (191) A sudden cessation of the menses had occurred three months previously. After that, her general condition had become much poorer She complained of hot or cold sensations and headaches, loss of appetite and palpitations Her condition improved again but three months later the patient once more had a violent chill lasting three hours, followed by heat sensations and a headache Two days later a pulse rate of 166, accelerated respiration and a temperature rise to 40° was recognized. At the same time the typical signs of Basedow's disease were discovered After two days the temperature went down to 38° and after another two days it had returned to *normal Also, the pulse rate had become lower and, in fact, sank, a week later, below* normal to 66 or 50 beats per minute All this occurred without any visible change in the goiter or exophthalmia Digitalis had already been discontinued for several days

disease, [illegible]
the neck and protrusion of the eyes was observed To these were then added the other major signs Death occurred after half a year In another case of acutely developing Basedow's disease in the case of a 20 year old man, Thingen (2597) noted, five days after the first occurrence of palpitation, shortness of breath and pains in the chest, a pulse rate of 100 to 144 beats, a temperature rise to 38 5° or 39°, and the typical signs of Basedow's disease An "insignificant catarrh of the lungs" could hardly be considered sufficient cause for the rise in temperature Serum therapy resulted in improvement of all symptoms

A 39 year old servant girl with Basedow's disease was presented by Gerhardt (2070) to the Society of Charity Doctors in Berlin There was a rise of temperature, at the beginning of the *disease, without any other cause After admission to the hospital* the temperature returned to normal, but in sharp daily rises. A temperature elevation has been found several times, by measurement, in isolated cases of Basedow's disease from the sixtieth year of the past century, as for example by Teissier (127),

Paul (174), Moreau (195), Birwinski (201), Cheadle (223 and 331), Lauder Brunton (329) Eulenburg (334), Samelsohn (441), Gluzinski (468), and Gueneau de Mussy (492) Bristow (646 and 648) reported a girl of 25 with a severe case complicated by ophthalmoplegia, (see §127) He measured temperatures of 38°, 39 6°, 40° and 40 3° during the entire period of observation with only occasional exceptions In the fatal case of a 32 year old woman, repeated temperatures of 39 5° to 40° were measured Fresh infectious changes were absent Only the signs of a past endocarditis were discovered

H Bertoye (748), a student of Renault in Lyon, had made temperature recordings consecutively on a number of patients He believed he could state that temperature elevation measurable by thermometer is very frequent in Basedow's disease He even spoke of a Basedow's disease fever, and distinguished between a strong form of long duration, febrile states, fever attacks of transitory nature, or a fever which is either continuous, remittent or intermittent He spoke of a fièvre inaugurale and a f cloturale (see p 359 above) When alterations in thyroid gland and eyes were only slightly, or not at all noticeable, a longer duration of the febrile state could, in Bertoye's opinion, offer an opportunity to confuse this with typhoid or tuberculosis Peter reports that he has seen cases of Basedow's disease which were wrongly believed to be pulmonary tuberculosis A Joffroy (1117) mentioned a case in which an obstinate cough combined with a rise in temperature gave rise to the supposition that it was pulmonary tuberculosis, until the nature of the Basedow's disease was definitely determined Fr Muller (2718), at the twenty-third Congress of Internal Medicine, made the statement that many cases had been presented to him of females believed to be anemic, with slight thyroid gland swellings, tachycardia, and palpitations When they became progressively emaciated, then started to sweat and to show a slight rise in temperature, with some coughing, they had been sent to a sanitarium in the belief they had an early pulmonary tuberculosis This later turned out to be Basedow's disease Thorbecke (2598) described such a case from Badenweiler A 38 year old woman, previously anemic and suffering from palpitation following an influenza, had spasmodic attacks of diarrhea and fever, and was much emaciated She was sent to the Black Forest because of an affection of the pulmonary apex Beneath the left lung slight dullness and prolonged expiration was evident, but there were neither rales nor coughing nor expectoration On the other hand the symptoms pointed to a Basedow's disease which, after temporary improvement, ended in death The autopsy showed a small, entirely healed focal area in the apex of the left lung

In a patient whose thermometer readings Bertoye had taken for two years, the fever type was such that abdominal pthisis was indicated Consequently a cold water treatment was given This caused the fever to cease The attacks of fever which recurred several times seemed to come at intervals corresponding to menstruation, although at the time this Basedow's disease patient was amenorrhoic

Wolfenden (800) declared that an elevation of temperature was constant in Basedow's disease Charcot (652), in 1856, said that it is the rule that in non-complicated cases not the slightest temperature elevation is added to the signs of redness of skin, abundant sweating, and a high pulse rate Three years later (817) he expressed the belief that Bertoye had definitely gone too far when he said that hyperthermia was a frequent occurrence in Basedow's disease Also the temperature elevations lack several essential characteristics of fever Furthermore, Bertoye, in his thesis, already pointed out certain differences of "Basedow fevers" from the usual complexus febriles Glunzinski (468), in 3 of his 15 cases, noted temperatures above normal In one fatally ending case the temperature rose to 38 4° a few days before death Lewin (777) mentioned one among 22 cases in which the axillary temperature rose to 38 8° without other cause Hector Mackenzie (918) usually had morning and evening tem-

peratures taken in his cases (more than 30), he found an increase only rarely. The temperatures were usually subnormal P J Mobius (4178, p 49 and 2717, p 54) considered it certain that Bertoye's data on the frequency of fever was exaggerated Among Kocher's (2197) numerous cases an abnormal rise in temperature was not noted in any of the non-complicated cases although 53 patients in the hospital were measured daily for several weeks or even several months Even those with strong subjective sensations of heat never showed a rise in temperature There was, to be sure, rise of temperature shortly before *exitus lethalis* after operations

In one fatal case reported by Askanazy (1690) death came from exhaustion. Temperature rises to 38° and 39 2° were observed several times in the course of the disease They lasted several days and could not be attributed to any local cause, although the patient complained now and then of rheumatic pains in the extremities and also, sometimes, of a painful swelling of the joints In a second case, which ended fatally, with signs of exhaustion and heart failure, body temperature rose to 39.8°, and temporarily to 40° with simultaneous tachycardia and mental and motor unrest without apparent cause beyond a slight bronchitis On the following day the temperature was normal again Bornikoel (2267) observed 2 soldiers with Basedow's disease but without a completely developed symptom complex Increased body temperature was noted over an extended period

Among 46 cases from the Breslau Medical Clinic (B Donchin 2644) only 3 showed a rise in temperature which certainly was not caused by a complication, none went above 37 8° and 38 2°

Of 43 among 80 Basedow's disease cases observed in the clinic and described by W Gilman Thompson (2773), 14 showed a temperature between 38° and 40°, in 7 it rose above 40°, and in all the cases the body temperature was above 37 5.° But Thompson at once added that 16 of these cases with more or less rise of temperature suffered from tonsilitis or pharyngitis or slight bronchitis

A few observers stated definitely that they had found the temperature normal. In cases with an acute course a pronounced rise in temperature had been observed more frequently Merklen (494) found it during an acute exacerbation of Basedow's disease in the case of a 27 year old servant girl With regression of the acute symptoms the temperature also became normal In Hardy's (546) case a temperature elevation was present during the development of the symptoms (see above) In 3 out of 4 acute cases and in one sub acute case reported in detail by Fr. Muller, consistent temperature readings showed only very slight irregular and temporary elevation up to 38°, at times above 38° and, just before death, 38 6° to 39 8° One case of severe Basedow's disease with acute course was a woman of 45 observed by E Reymond (1143) The body temperature, with a pulse rate of 125, rose to 40° before death In Spencer's (1662) acute case of a 16 year old girl, death occurred with high rise in temperature and stormy heart action In the case of a 21 year old girl with severe acute Basedow's disease reported by Hirschlaff (1733), daily, irregular, temperature fluctuations occurred A maximum above 38 5° was noted sometimes in the morning, sometimes in the evening Shortly before death the temperature rose to 39 8°. Among 6 more or less acute fatal cases which Röper (1911) described from Curschmann's Clinic, spasmodic temperature rises to 37 8° and 38 8° were found, one of them, before death, reached 39 6° with a pulse rate of 130 to 160. In one of the cases the autopsy revealed a fresh pleuritis, pericarditis, and *endocarditis verrucosa*. In one very severe case with an acute course, a female of 33 observed by Arneill (1934), death occurred following a temperature rise to above 41° and a pulse rate over 200. Dinkler (1953) noted, in the case of a 41 year old woman, during a severe relapse of Basedow's disease which led to death after three months, temperatures of 39° with heavy, rapid breathing Pulses

up to 200 were registered in the last week In the case of a 43 year old man with severe Basedow's disease Brucner (1944) noted acute mental confusion, hallucinations and temperature rise up to 40° during the final period before death In a very acute case, with uncontrollable vomiting and severe nervous symptoms (see §135, above), observed by Diller (2169), a woman of 46, body temperature rose to 38 5° and, before death, to 39 5° The pulse rate registered from 130 to 140 In a case with a very acute course, that of a 55 year old man described by Atkinson (2254), delirium, tachycardia up to 140, and considerable rise in temperature preceded death In a severe case of a 50 year old woman with Basedow's disease, observed by Klein (2393) three days before death, a rise of the previously normal temperature and a rapid loss of strength was evident With advent of bulbar signs (see 129 above), tachycardia above 160, and dyspnoea, the temperature rose to 40 7° The end occurred during a profound coma J Rogers (2763) reported a woman of 29 with acute Basedow's disease The temperature reached 40° the pulse rate 136 and the respiratory rate 38 In the acute, fatal cases of Humphry (2518) and Matson (2542), temperature rise was moderate, between 38° and 38 5° A very severe case of Basedow's disease, a 30 year old male described by Chevalier, had no temperature rise, or only a few tenths of a degree in spite of distressing cardiac sensations

Th Kocher (2693a) has recently stated that in all severe cases of Basedow's disease the postoperative reaction is much more severe than that following the excision of a common, or even of a malignant goiter It occurs as a sudden rise in temperature and a rapid acceleration of the heart which cannot be satisfactorily explained by the resorption of a large hematoma This view of Kocher's has, to be sure, been contradicted by others on the basis of clinical results and with reference to experiments on animals (By Riedel 2334, Lanz 2093, Pässler 2559, K Schultze 2881 and others)

To speak of fever in connection with a rise of temperature in Basedow's disease, as many authors do, seems to me entirely unjustified Charcot (817) himself emphasized that the hyperthermia of Basedow's disease patients lacks several important criteria for fever, and the urine, in particular, does not have the characteristics of a fever urine Bertoye (748) admitted that heat sensations, sweating and tachycardia stand in no relation whatsoever to the elevation of temperature All of these manifestations, except in severe acute cases, may be moderate at the height of the temperature rise and may be well developed while the thermometer reading is normal or only slightly elevated The loss of appetite of those with fever is also absent in most cases of Basedow's disease Gilles de la Tourette and Cathelineau (829) point out that among patients with Basedow's disease the volume of urine, reckoned by kilogram of body weight, does not, even at elevated temperature, vary to any notable degree from normal In one case, in which the temperature was higher for a period of time and temporarily reached 39 2°, the urine did not show any variation in qualitative character, and urea, phosphoric acid and urobilin were in normal proportions

In the metabolism of the above-mentioned conditions we see a fundamental difference between the hyperthermia of Basedow's disease and

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an increase in oxidation processes, and that the participation of a heat production regulating apparatus is not excluded. Aronsohn believed (2605) that even the increased protein breakdown which follows this heat center lesion, as in fever, is under nervous control Krehl (2395) and his pupils, as well as C. Hirsch and Rolly (2294) observed a contradictory reaction between fever and the warmth of this experimental hyperthermia The source of heat production in the first case is chiefly nitrogen-containing material, but in the latter it is almost exclusively nitrogen-free matter This breakdown takes place not *only* in the muscles, *the liver with its abundance of glycogen also plays an essential role No temperature rise occurs following the experimental brain lesion* (Rolly 2294) without glycogen in the liver The increased protein catabolism is only a secondary result of the body warmth. P. Fr. Richter (2733), however, could not confirm that the rise of body temperature following the heat center lesion was absent with glycogen depletion or complete lack of glycogen in the rabbit Fr Kraus (2698) felt certain that, in principle, the temperature elevation is not dependent upon the presence of glycogen in the animal body

However that may be, we must ask ourselves whether the increased protein breakdown found in many cases of Basedow's disease should not be regarded as a result of hyperthermia Aronsohn (2605) said that after perusing the pertinent literature, he had become convinced that an increase in protein turnover occurs in Basedow's disease only when fever or excessive nervous excitement play a part That is definitely not correct In just those cases in which Fr Muller made his first exact metabolism experiments in Basedow's disease and showed an increased protein breakdown this same careful investigator (1134, p 363) added expressly: the body temperature was normal during the tests, 36 8° to 37 6°, the pulse between 140 and 168, the respiration 36 to 50 Four months before the beginning of the experiment temporary temperature rises of 37 8° to 38 8° occurred The extremely acute case of Chevalier (882), in which certainly an increased N_2 breakdown occurred, registered no fever Furthermore, we must unfortunately admit that in most cases in which metabolism experiments have been carried on during Basedow's disease not enough attention was paid to the body temperature

Among human subjects suffering from overheating because their heat dispersal is impeded, an increased protein breakdown has been observed, which cannot be limited by any corresponding large intake of carbohydrates But this occurs only when the body temperature reaches 40° or more. We are therefore justified in explaining the protein breakdown in this manner only in those rare cases of Basedow's disease in which the body temperature reaches 40° or more. Even then, only a limited part of it is accounted for directly by the temperature rise In the much more

that of fever. In Basedow's disease, as we have shown, the total oxidation processes are always more or less accelerated and the protein breakdown is either considerably below that of fat or is entirely absent. In fever, on the other hand, we know from the investigations of Fr. Kraus[1] that a rise in total oxidations is not necessarily one of its characteristic features, while an increased breakdown of body protein is never absent; indeed it is the characteristic feature of fever metabolism.

Experiments by May on rabbits and by Stakelin on dogs have consistently shown that in fever the oxidation processes can be increased Observations on humans have shown that O_2 consumption and CO_2 output have exceeded the normal values for the individual in some cases but not in others Rises of from 50% to 70% above the normal for fever are, as Kraus (2698) very correctly emphasizes, to be attributed to simultaneous muscular activity If this is subtracted the remaining net value by which the oxidation process has been increased by the fever is rather insignificant. At any rate there is no direct parallel between the height of the fever and the oxidation processes in humans, while in Basedow's disease the gas exchange experiences such a considerable increase that it can no longer be explained by muscular activity alone

The consequence of the total oxidation processes in Basedow's disease is a corresponding elevation of the heat of combustion. But as long as those remarkably delicate and reliably functioning mechanisms which keep the production and output of heat warmth in exact balance are not damaged, great muscular activity still does not raise the body temperature of healthy persons, even though the total oxidations is increased to a still higher degree In the majority of cases these regulating mechanisms in the course of Basedow's disease are functioning so well that overheating does not occur The blood vessels of the skin are enlarged, at least in certain regions of the body. The skin is continually moist, and often perspires profusely as great amounts of heat are given off Troublesome heat sensations cause the patients to dress lightly and to expose their skin to the air. Increase in the rate of respiration liberates more moisture and heat through the lungs. The proper functioning of these regulation mechanisms depends upon the state of certain centers in the cerebrum We have become acquainted with the most important of these centers through the investigations of Aronsohn and Sachs[2] on rabbits

These investigators have shown, and many others have since confirmed, that a lesion on the medial border of the *corpus striatum* in the posterior portion of the protuberance into the lateral ventricle is associated with a considerable rise in temperature. Aronsohn believes this rise is caused by

[1] Uber den respiratorischen Gaswechsel in Fieber", Zeitschr f. klin Medizin, XVIII, p 160.

[2] Die Beziehungen des Gehirns zur Korperwärme und zum Fieber; Pflüger's Archiv f d. ges Physiologie, XXXVII, p 232, 1885

Mannheim (1222), in only 21 among 47 polyclinic cases, gives data concerning the nature of the blood; in 10 the presence of anemia is noted; 9 of these showed simultaneous emaciation and debility. In 10 the absence of anemia was expressly emphasized, 3 of these patients were emaciated In 1 case, a 19 year old girl, chlorosis was conspicuous Pässler (1362) in 34 among 51 polyclinic patients with Basedow's disease (that is, in 66 7% of his cases) noted pallor of the skin and the visible mucous membranes Kroug (2700) never found a normal skin or mucous membrane coloration among his 106 Basedow's diseased patients A large number showed distinct evidence of anemia, at least according to the clinical signs Rachlmann (634) was impressed in several cases by the bright red color of the blood in the retinal vessels among several cases in which pallor of the skin and visible mucous membranes were conspicuous (see §71 above)

An anemic condition not infrequently becomes evident among the early signs of Basedow's disease, together with emaciation. It often precedes the other signs by several months An obstinate anemia, the cause of which appears uncertain, may be followed in quick succession by the other signs of Basedow's disease

Nevertheless, it would be quite mistaken to draw the conclusion from such observations that the anemia stands in a casual relationship to Basedow's disease Keen observers, such as M. H. Romberg (39) and Trousseau (128), have already recognized and stated very early that anemia is only an accessory sign of Basedow's disease and that cases occur in which, notwithstanding the most careful examination, the characteristics of anemia cannot be discovered

The examination of the blood shows little or no variations from normal, in the majority of cases, in respect to the relation of the red to the white corpuscles and the percentage of hemoglobin, even with pronounced cachexia In so far as the total volume of the blood is more or less reduced one can speak of a relative anemia (Kroug 2700).

Oppenheimer (856) found a woman of 23 and a woman of 35 who had Basedow's disease for a long time, looked pale and poor in blood, and who showed a very conspicuous symptom complex of the disease Yet the values for hemoglobin were in content 95%, and 90% of normal, respectively, and the specific of gravity was 1 057 The number of red blood corpuscles per cmm was 4,150,000 to 4,350,000, figures which also approximate the average for the female sex Fr Muller (1134) undertook a blood test in the case of a 25 year old woman suffering from severe sub acute Basedow's disease and markedly reduced weight three weeks before death The count of the red corpuscles was 4,600,000 Otherwise the blood showed no marked changes Zappert (1165) studied a 25 year old female patient with Basedow's disease He found 3,658,000 red and 8,200 white blood cells per cmm and, in the case of a healthy 16 year old girl, 3,984,000 red and 7,300 white, in that of another healthy 16 year old girl, 4,120,000 red and 7,200 white corpuscles, furthermore, in the case of a 30 year old healthy man he found 5,480,000 red and 6,400 white corpuscles Pässler (1362) records the results of an examination of the blood of 2 Basedow's disease patients whose appearance gave no indications of anemia, and 4 others with pallor of skin and the visible mucous membranes The counts of the red cells were 4,300,000 and 4,665,000, and of the white

numerous cases with lower or nearly normal temperatures, we must probably attribute this breakdown to direct toxic action on the body cells, and in this sense we are justified in speaking of a toxogenic protein breakdown.

The chief source of the chemical breakdown from which the surplus heat in hyperthermia in Basedow's disease originates is doubtless the nitrogen-free substances, and among these mainly body fat.

We may probably assume that to stimulate heat production in Basedow's disease a central toxic-chemical stimulus such as the heat center lesion is important. With a greatly overbalancing heat production, the central regulating mechanism controlling the emission of excess heat seems absolutely or relatively insufficient. It is still uncertain as to how we must picture the influence of the center for increased heat production and the nature of the control of such breakdown by the central regulating mechanism. The fluctuation in temperature elevation in Basedow's disease as well as its susceptibility to mental excitement points to the central nervous system. The statements above have defined the place of the temperature rise in Basedow's disease among the various hyperthermias. This is in contrast with fever in which, as Kraus expressed it, the temperature of the organism is regulated to a higher level The Basedow's disease hyperthermia shows a certain lability and thereby approaches more closely the heat center lesion hyperthermia It also resembles those temperature elevations which we observe, for instance, with certain lesions of the *medulla oblongata* and following many injuries to the cervical spinal cord. In such cases we have to locate the actual center of heat regulation in the midbrain, and to think of these as stimulated by the areas of heat production in a manner similar to that by which the vascular centers can be influenced from a great variety of points in the nervous system.

The so-called hysterical fever cannot serve as comparison here, since such an important voice as that of Strumpell[1] doubts its actual existence.

The Blood Picture

§226. Anemia to a greater or lesser degree is a frequent accessory sign of Basedow's disease. It usually goes hand in hand with emaciation and debility. The skin in Basedow's disease as a rule appears pale The face sometimes, in striking contrast, is a brilliant red (see §154 above)

Squire (681) considered anemia to be one of the most conspicuous signs of Basedow's disease J Russell-Reynolds (932), in all but one of his 49 Basedow cases, found a distinct anemia which, he adds, cannot be distinguished from ordinary anemia

[1] Deutsche Zeitschr f. Nervenheilk XXX, p 953, 1906.

Zappert (1165) reported a 45 year old female Basedow's disease patient with pronounced signs of anemia. He counted 2,858,000 red blood cells to 3,800 white ones, and in the case of a 15 year old girl with Basedow's disease and chlorosis, 2,736,000 red to 3,800 white cells In the case of a 39 year old woman with Basedow's disease and conspicuously dark gray coloration of the skin of the face, hands and feet Vorster (1257) found the number of red blood cells reduced to 1,844,000 per cmm and the hemoglobin content reduced to 22% with a specific gravity of 1,031 A drop of blood exuded from a finger stab had a pale, chocolate brown coloration Vorster expressed the supposition that perhaps the pigmentation of the skin had some relation to the impoverishment of the blood in erythrocytes and hemoglobin Mesowicz (2413), in the case of a 20 year old greatly emaciated female Basedow's disease patient with continuous vomiting, measured a hemoglobin content of 57% and estimated the count of red corpuscles per volume unit to be 3,800,000 R. Wybauw (2139) described 2 cases of Basedow's disease with excessive anemia in women of advanced age, the red cell count as well as the hemoglobin content was greatly reduced Among the 52 cases of typical Basedow's disease which Landström (2849) assembled, a 40 year old woman had a red-cell count of 2,900,000 and very low hemoglobin content Two of Kocher's cases with abnormally low blood counts we have mentioned above.

Schur (2751) made numerous red blood cell counts on a Basedow's disease patient who showed nothing noticeable beyond the typical signs of the disease During a long investigation, and later in a blood sample obtained after death he found minute bodies of varying size which were easily stained with basic stains These small bodies were not identical with the blood platelets nor with the pyrodin poisoning inclusions which occur in the red cells Such bodies, the nature of which is entirely unexplained, were not found in the studies of other patients with the disease

For an example of high grade anemia associated with enlargement of the spleen in a typical case of a four and a half year old boy with Basedow's disease, see Variot & Roy (2132).

§227. Recently attention has been directed to exact investigation of the various forms of white blood cells.

Zappert (1165) studied the relation of the number of eosinophil cells to that of the white cells among 4 Basedow's disease patients and in a number of healthy persons In the latter, the count of the eosinophils fluctuated between 55 and 784 per cmm, usually between 55 and 275, in the patients afflicted with Basedow's disease it was between 100 and 697 The latter, an unusually high count, was found in the case of a 15 year old girl with 3,968,000 red and 8200 white corpuscles per cmm The proportion of the eosinophils among the white cells was 8.5% In the case of a 35 year old male patient with Basedow's disease and with normal blood the relation was 145 to 4200, *that is 3 45%. In 2 plainly anemic cases it was 3800 to 100, and to 230 respectively,* giving 2 63% and 1 63%

Ciuffini (2632) in the cases of 6 patients with Basedow's disease measured a marked reduction in the proportion of the neutrophil polymorphonuclear corpuscles, usually a nearly normal count of eosinophils and basophil polynuclears, and an increase in mononuclear leucocytes, especially the medium and larger ones The red cells he found were usually rather numerous but with moderate reduction in the hemoglobin content

Th Kocher (2693 and 2940) reports that in many cases of Basedow's disease he had the blood microscopically examined by his assistants Dr. v. Steiger and Dr. Nageli in Zurich are especially experienced in this

cells 10,600 and 11,500 Also, in the cases in the second category, completely normal conditions were shown a man of 22 with severe Basedow's disease had 4,635,000 red and 6,000 white corpuscles, a woman of 32 4,500,000 red and 11,200 white; a man of 32 4,000,000 red and 11,500 white, a woman of 27, 4,900,000 red and 7,800 white blood cells The hemoglobin content in 4 of these cases was 70 to 75%, in one 85%, and in one with clinical indications of anemia it was actually 90% Microscopic examination showed no variations from the normal state either in the fresh or in the stained specimens All tests were made before the noon meal W Scholz (1377) found a normal blood picture in the case of a 29 year old woman with typical Basedow's disease The hemoglobin content was 80%, with 4,800,000 red and 6,000 white blood cells per cmm A blood test was made in all of Kocher's (2197) cases which remained under observation for some time The hemoglobin content seldom went below 80%. The count of the red cells remained, as a rule, above 4,000,000 Only in 2 cases, neither one of which was extremely emaciated, the red-cell count declined to 3,680,000 and 3,800,000, with normal white cell content H Mackenzie (2537) had the blood examined in a series of cases of Basedow's disease and obtained normal results. In the acute fatal Basedow's disease case of a 32 year old woman, reported by L Humphry (2518), the blood count showed 6,250,000 red and 4,500 white corpuscles In a few of my own cases

ence severe cases of Basedow's disease with pronounced cachexia had changes in the composition of the blood but no actual morphological alterations of the red cells.

In various kinds of anemia, and also in 8 female patients with Basedow's disease H Rosin and S. Jellinek (1982) have determined not only the blood count and hemoglobin content, but also the iron content as measured by the ferrometer of Jolles (Vienna). The iron content by no means always agrees with the hemoglobin content Values often differ considerably Sometimes the iron content, and sometimes the hemoglobin content is greater The investigators had previously assured themselves as to the reliability of the apparatus in Basedow's disease. It was evident that the hemoglobin readings showed high values with a normal count of red cells per unit volume and an iron content more or less below the normal.

In the case of a 60 year old female Basedow's disease patient the hemoglobin content was twice as great as the iron content In the case of a woman of 27 and a woman of 47 the former was normal (100%) These results approach those found in icterus *In other forms of anemia the hemoglobin content and the iron content were abnormally low* First one, then the other was greater In chlorosis the hemoglobin content as well as the iron content is below normal and the number of red corpuscles varies The color value of the blood was abnormally low only in 2 cases of Basedow's disease, corresponding to a hemoglobin content of 68% and 50% respectively Their observations of patients with Basedow's disease led these two investigators to believe in the possibility that unknown pigments circulate in the blood in this disease The serum was often found to be abnormally dark.

Cases of Basedow's disease in which the number of red cells is considerably reduced and the hemoglobin content unusually low are found only rarely in the pertinent literature.

Between the typical and the incompletely developed form of Basedow's disease Gordon and V Jagic could find only a gradual transition in the blood picture (see, more exactly, §244 below).

Kocher (2940) has gained the impression that in those cases in which the total count of white blood cells has increased only slightly or not at all, a higher percentage of lymphocytes seems to be of less serious significance, prognostically, *than in those where the reduction of the total count* of white blood cells is considerable The lymphocytosis seems to be less pronounced in the early stages of the disease than at its peak. Operative measures can influence the blood picture considerably.

All of these results of blood tests indicate, according to Kocher, a certain analogy between the severe cases of Basedow's disease and the so-called *status lymphaticus* (see §229 below) In both conditions, any kind of surgical interference carries with it a danger of sudden death, especially when special conditions, such as narcosis, are brought into the picture According to Nägeli, chronic lymphocytosis and eosinophilia are characteristic features of chronic infections and poisonings

A highly significant finding appears to have been made by Fr Kraus and Friedenthal (2942). In almost all the cases of Basedow's disease tested, they demonstrated that the blood had an epinephrin-like power to dilate the pupils of enucleated and illuminated frog eyes

Nine cases with the typically developed symptom complex showed almost constantly a distinct, completely positive reaction Also, in 2 goiter patients with *Basedow's disease signs the reaction was weakly positive In contradiction to this the* blood of 3 patients with a neurasthenic or hysterical cardio-vascular neurosis had no mydriatic influence

These results correspond to the facts discovered by the aforementioned investigation showing that in animals an epinephrin effect can be produced in the peripheral blood by the intravenous injection of thyroid extract

§228. Frequently there is more or less anemia associated with Basedow's disease, but rarely do we find the typical picture of chlorosis.

When present, it usually involves young girls between 15 and 24. Chlorosis always precedes development of the Basedow's disease signs by months or years In the majority of the cases these are the milder forms of Basedow's disease. Often the symptom complex remains incomplete, most of the eye signs are absent The manifestations of the chlorosis become more prominent in the disease picture Sometimes the development of Basedow's disease signs will follow rapidly or acutely (v Noorden 1629) Their remission usually goes hand in hand with improvement in the anemia Iron preparations as well as chalybeate springs which uncomplicated cases of Basedow's disease do not tolerate well, seem to be helpful.

As early as the middle of the past century, Wunderlich (60) called attention to the fact that, among chlorotics, not infrequently a slight swelling of the thyroid gland

Most typical cases showed an increase of lymphocytes and a reduction in the count of the polymorphonuclear forms among the white cells, up to 60% of the latter. In one case investigated by Nageli even 74% of mononuclear forms were found The usual proportion is 30% to 40% With this, there was no increase at all in the number of the leucocytes. Their total count corresponded, as we have emphasized above, about to the normal, although sometimes it was greatly reduced. Among the lymphocytes there is found a number of atypical forms with large nuclei and rather abundant protoplasm Nageli also found in several cases 2 or 3 myelocytes associated with this reduction in the neutrophil polymorphonuclear cells and slight reduction in the count of the red cells.

Our previously described (§214) case of peculiar skin thickenings on both lower legs had a blood analysis undertaken for me by Dr. Stadler. The result was an almost normal count of the white cells; 62.2% were *polymorphonuclear neutrophil leucocytes, 30% were lymphocytes, 3%* were eosinophil cells, and 4 8% were myelocytes I do not venture to decide whether this fact can be brought into relation with the changes found on the tibia.

E Meyer (2950) found, in the cases of 2 Basedow's disease patients, a lymphocytosis of 40% and 86% respectively The blood condition was not constant in these patients, however.

Caro (2812 and 2907) noted among clear-cut cases of Basedow's disease only a slightly reduced hemoglobin content and an about normal count of red cells With this, there was a reduction of the polymorphonuclear leucocytes to 50% and a great increase of mononuclear forms and lymphocytes

In cases of thyroidism a parallel but less marked alteration of the blood picture was evident After the feeding of thyroid-gland preparations an increase in the number of mononuclear cells occurred Improvement in the Basedow's disease was associated with a restoration of the blood findings to normal

As a result of their blood tests on patients with Basedow's disease J. Gordon and N V. Jagic (2923) emphasized the almost constant occurrence of lymphocytosis which they termed "mononucleosis" They considered it far more characteristic than the occasional leucopenia. The red-cell count as well as the hemoglobin content were usually found to be normal.

From these findings and from the condition of the blood-forming elements arising in the bone marrow the conclusion may be drawn that there is no essential damage to bone marrow function in Basedow's disease. The reverse is shown by the lymphocytosis present in almost all the cases, the increase of the mononuclear leucocytes indicates an abnormal reaction of the lymphatic system (see §229 below).

by blood examination and it continued. In her twenty-first year, during an attack of perityphlitis, cardiac palpitation began Tachycardia up to 200 beats per minute occurred Six months later a swelling on the neck and protrusion of the eyes became evident. In this patient, furthermore, a pronounced predisposition to Basedow's disease was present, for an older sister also suffered from a severe form of this disease In the case of a 20 year old woman the signs of Basedow's disease developed gradually, in association with chlorosis The patient came from a nervous family A brother had Basedow's disease. In 4 other cases, according to the case histories, the chlorosis came first.

v. Noorden (1629), in 7 among 255 chlorotics, found the complete pattern of Basedow's disease, goiter, tachycardia, palpitation, tremor, sweating, muscular unrest and mental excitement, 4 times goiter, tachycardia, tremor and hyperidrosis, 7 times the latter symptoms without thyroid enlargement; 5 times tachycardia and tremor, 3 times tachycardia and hyperidrosis, 3 times tachycardia with goiter, and 5 times a vascular goiter without signs of thyroidism In a few patients these signs outlasted the anemia, in other cases chlorosis was present only at the peak of their development

A 22 year old girl had anemia several several times, once in association with a swelling of the neck During a new attack of severe chlorosis the signs of Basedow's disease appeared with unusual rapidity In two weeks time the chlorosis had reached its peak, there was profound muscular weakness but no trace of a goiter Two days later the circumference of the neck had increased by 4 cm, the pulse rate had risen from 80 to 106, and the eyes protruded noticeably In the two following days the goiter grew still larger, pulsated and had a vascular *bruit*, the exophthalmia increased, the patient sweated continuously, trembled, was sleepless, and felt extraordinarily weak With this, the peak of the disease was reached From the following day on all of the signs rescinded and five days later they had vanished The neck circumference returned to its former size of 34 cm, and the pulse rate again was 74 per minute

A swelling of the thyroid gland was found by Giudiceandrea (2376) in 57 among 70 cases of chlorosis which were examined for it, that is, in 81 43% of the cases Among 42 cases of anemia of medium severity the enlargement of the thyroid was distinct in 16, and in 4 more it was marked Among 28 cases of severe chlorosis an increase in *the size of the glandula thyroidea was very distinct 14 times, and marked in 13 others* Among 57 anemics in whom a thyroid swelling was distinguishable 35 were free from Basedow's disease signs, the other 22 rather severe cases showed tachycardia eye signs and tremor The 13 cases in which no trace of goiter could be discovered were simply mild forms of chlorosis.

Some connection between anemia and Basedow's disease signs with a mild or severe degree of thyroidism can probably be denied in the light of the observations just recorded. v. Noorden (1629) believes that substances are given off from the ovaries by internal secretion to stimulate blood formation, especially in the bone marrow, and thus to compensate *in a normal manner for the monthly loss of blood. On the other hand* it is undeniable that a relationship exists between the internal secretions of the ovaries and the thyroid gland. I recall the well-known fact that not infrequently even in healthy girls and women a measurable increase in the size of the thyroid gland occurs shortly before the beginning of menstruation The relatively frequent occurrence of thyroid enlargement in anemia forms a bridge for the connection of the two diseases to one another. It is quite

is evident and, in some cases, a peculiar protrusion of the eyeballs occurs Immismann went further In his treatise on general nutritive disturbances he stated that an unmistakable etiological relationship exists between chlorosis and Basedow's disease But in the second edition of his work (434) he admitted that a direct connection between Basedow's disease and anemia seems improbable in those cases in which the former arises during the presence of a chlorosis. There are not a few cases of Basedow's disease which etiologically have nothing whatsoever to do with the chlorosis Beni-Barde (296) supposes that many chlorotics are attacked by Basedow's disease But Tessier (127) has explained that, although goiter and anemia are rather common maladies in Lyon, those who are acquainted with Basedow's disease and study it *carefully will not mistake a combination of goiter and the symptoms of chlorosis* for Basedow's disease

Fr Chvostek (1096) reports 7 cases from the II Medical Clinic in Vienna in which the signs of Basedow's disease appeared together with typical chlorosis The patients were between 15 and 22, they were of slender build but not emaciated; in a few the fat layer was rather fully developed The skin and the visible mucous membranes displayed the characteristic pallor The number of red blood cells was considerably reduced, in one case, a girl of 15, to 2,736,000 per cmm, otherwise they fluctuated between 2,900,000 and 4,000,000 There was usually no leucocytosis, only in the case of the above-mentioned 15 year old girl the count of the white corpuscles was reduced by 20 to 45% Menstruation had ceased recently or it came at greater intervals and was scanty In the case of a 19 year old girl it was, on the contrary, more profuse for a week The patients complained of palpitation, debility, headache and sweating Blowing murmurs could be heard over the heart, pulse was rapid (92 to 120) There was distinct carotid pulsation The thyroid gland was only moderately enlarged in all cases, only in two cases systolic blowing *bruits* were audible over it Exophthal-

[illegible]
of the knees when walking

G F Johnston (1120) reported 2 such cases A well-developed young girl with all the symptoms of a chlorosis had slight uniform swelling of the thyroid gland, pulse *of 120, distinct exophthalmia, von Graefe's sign, slight tremor of the hands*, and amenorrhea for several months A 19 year old definitely chlorotic but not emaciated woman complained of headache, weakness, inability to work, and palpitation She had a pulse rate of 110 beats per minute and marked exophthalmia, but no lid signs or tremor

Zappert (1165), in the case of an extremely anemic girl with Basedow's disease, counted 2,736,000 red and 3800 white corpuscles, including 230 eosinophiles In the case of a 19 year old girl with chlorosis and signs of Basedow's disease Passler (1362) determined the hemoglobin content as 50% of normal

Maybaum (1374) reported a 20 year old girl from the Gerhardt Clinic She had been chlorotic since her 14th year and recently showed signs of Basedow's disease. Only the eye signs were absent. The count of red cells was 3,250,000, of white 16,000 per unit volume

In a case reported by Hayem (1582) chlorosis was combined with symptoms of hysteria and Basedow's disease According to this observer enlargement of the thyroid gland occurs in about 82% of chlorotics

Among Kocher's (2197) abundant observation material 2 cases developed Basedow's disease in connection with chlorosis. In the case of a 23 year old girl anemia appeared at the beginning of menstruation in her fourteenth year The chlorosis was verified

palpable goiter; in another the lymph glands could only be felt after the goiter had become visibly smaller. Passler has remarked that he has seen swelling and vascular engorgement in the above mentioned lymph-node *clusters at the post mortems of persons who had a goiter but no definite* Basedow's disease. Mattieson (1471) has stated that in 3 cases many small lymph nodes could be felt on the neck.

Kocher (2197 and 3693) has paid special attention to these discoveries. He explains that, in Basedow's disease, the perithyroidal lymph nodes which correspond to the lymphatic drainage of the thyroid gland are nearly always found to be hyperplastic, at least upon operative exposure. Their size varies between that of a pea and that of a bean. Microscopic examination shows the lymph glands removed at a goiter operation to have *marked hyperplasia. Palpable enlargement of other lymph-node groups* were found in only a few cases Slight swelling in almost all the lymph nodes was found by Kocher in only 1 case, a woman of 44 In 2 cases the tonsils were hypertrophic and there were adenoid growths in the nasal cavity. Only once a non-pulsating enlargement of the spleen was encountered One other case with chronic enlargement of the spleen had a history of malaria. I, myself, in a case of Basedow's disease of a young girl observed over a long period, saw a rapid development of lymph-gland swelling on both sides of the neck about one year after the beginning of the disease This arose without pain and without evidence of local disease It disappeared again after a few weeks No noticeable change in the disease pattern occurred during this time I cannot decide whether a hyperplasia of both tonsils, observed two years later, which led to their removal should be considered to be closely connected with Basedow's disease The general condition was less good at just that time, but there was no fever

An acute fatal case of Basedow's disease was described by Hirschlaff (1733) The patient was a 21 year old woman. The autopsy disclosed numerous swollen lymph glands in the neck, marked follicular hyperplasia of the tonsils, follicular hypertrophy in the spleen and intestine; a large persisting thymus of fetal structure was found in the anterior mediastinum Hirschlaff adds expressly: "Since an infection as cause of the hyperplasia of the lymphatic system in all the organs could be excluded this must be attributable to a toxin which, in a manner analogous *to the toxins of infectious diseases, produced the changes in the lymphatic* organs" Swelling of the intestinal follicles and tonsils has also been seen a few times in Basedow's disease

Gluzinski (468) found, in the typical case of Basedow's disease of a 41 year old woman, hypertrophy of the solitary and Peyer's follicles and enlargement of the spleen Savage (568) mentioned, in the case of a 28 year old woman, hypertrophy of the Peyer's patches C Higgins (662) observed, in the case of a 29 year old girl who

certain that some additional not clearly defined factor must arise in order that the symptoms of thyroidism are added to the pathological enlargement of the thyroid gland.

Condition of Lymph Glands and Lymphoid Organs

§229. W R Gowers (766 and 1042) first called attention to the fact that, sometimes, enlargement of the lymph glands occurs in the course of Basedow's disease This can develop rapidly and disappear again slowly He has seen three examples of this. One was a fatal case of Basedow's disease involving a girl whose sister suffered from lymphadenoma.

Gueneau de Mussy (492) had been impressed long ago by the fact that, in 3 out of 4 cases of Basedow's disease which he had observed, the right tracheal and bronchial glands were swollen Hutchinson (271 and 664) reported Basedow's disease in the case of a child, several lymph nodes were enlarged and, furthermore, there was a *swelling of the lachrymal glands and the parotid, while a goiter was absent.* More exact data are lacking and it is not possible to decide whether this has any connection with Basedow's disease

Fr Muller (1134) found, at the post mortem of 3 severe cases of Basedow's disease with an acute course and of one with sub-acute course, that the lymph glands in the region of the thyroid gland and around the large vessels and nerves of the neck were enlarged, and blood was red. The microscopic examination showed hyperplasia of the lymphoid tissues, distention of the blood vessels, and old and new hemorrhages in the cortical layers. Following these autopsies, Fr Muller took notice in all Basedow's disease cases coming under his observation of the occurrence of lymph-node enlargements in the neck and found them constantly. In *several cases of severe Basedow's disease there were, at the time of exacer*bation of the disease, hard knots palpable on throat and the back of the neck the size of beads, lentils or peas.

Fr Muller did not hesitate to believe that these lymph-node enlargements were frequent or constant occurrences in Basedow's disease. Two years later he said (1624 b.) "almost constantly there are found in Basedow's disease numerous small swollen lymph glands on the neck These are usually smaller than those seen in syphilis, and often are arranged like beads on a chain " They are found not only in fully developed Basedow's disease but are also seen very frequently in association with the parenchymatous goiter of the youthful individuals in whom Basedow's disease signs are often found Passler (1362) found in 11 among 51 polyclinic cases of Basedow's disease that the lymph nodes in the neighborhood of the thyroid gland, especially in the supraclavicular hollow, and on the neck, were hard and swollen In one of these cases there was a

which produced no visible changes in the gland but altered its function to the extent that secondary lymph-node enlargements, a disturbance of cardiac function and of the general nutritive and cerebral malfunction took place

Glycosuria and Diabetes

§230. A peculiarity of Basedow's disease only recently studied and considered important is the relatively frequent occurrence of glycosuria as evidence of definite disturbances in the carbohydrate metabolism

In healthy persons the utilization of sugar, that is, that amount which can be taken without causing glycosuria, is variable This is true for different individuals as well as for the various kinds of sugars, and for the same individual at different times In particular, the differences depend on whether the sugar is taken alone or following a meal In the first case small amounts of fructose are sufficient to produce glycosuria, but the threshold is usually rather high. According to v Noorden the physiological limit of assimilation of fructose taken into an empty stomach lies between 180 and 250 gm Therefore, one can only speak of a pathologically increased alimentary glycosuria if it is produced by amounts of fructose less than 180 gm.

In regard to the frequency of occurrence of an increased alimentary glycosuria in Basedow's disease the experimental data vary greatly with different investigators. The cause for this may be found in differences in the experiments

F. Kraus (984) and F Chvostek (1030), for instance, gave 150 to 200 grams of chemically pure fructose (Kahlbaum preparation), dissolved in 200 cc of hot tea This was made palatable by the addition of some cognac, and served very soon after a noon or evening meal excluding carbohydrates They then tested each spontaneously voided and separately collected specimen of urine during the following 24 hours for the presence and amount of sugar Goldschmidt (1442) and H Strauss (1663) gave 100 gram of dry fructose (Kahlbaum) dissolved in 500 ccm of water This was taken on an empty stomach The persons undergoing the experiment collected urine hourly during the following 4 or 5 hours of fasting The separate urine specimens and the urine of the preceding night were examined for sugar The results were regarded as positive only when the fermentation test produced a positive reaction

Hirschl (2675) proposed that, for practical reasons the examination for alimentary glycosuria be simplified, so far as the exact determination of the assimilation limit for fructose permitted. One simply gives the patient every morning after breakfast 100 gm of chemically pure fructose (Kahlbaum). The urine of the following 24 hours is collected, and the sample examined for fructose by polarizing, afterward allowing the sugar to ferment for 24 hours and polarizing once again. The difference in the two results gives the fructose content of the urine Alimentary glycosuria

had Basedow's disease for more than 10 years, and who died under anesthesia, general tendency to lymphoid hypertrophy and growth of lymphoid tissue in the thymus

... dark red and en-larged, and there was a 60 gm thymus vestige Abram (1259) saw in 2 cases on which he performed an autopsy that the intestinal follicles were hyperplastic Furthermore, he reports 2 cases in which a marked enlargement of the tonsils appeared after the outbreak of Basedow's disease Among 4 post mortem reports contributed by Farner (1429), enlargement of the lower cervical lymph nodes was noted once in the case of a 23 year old woman who had died of pleuritis and pericarditis, and once in the case of a 18 year old girl who had an enlargement of the tonsils, of the follicles at the root of the tongue, of the intestinal follicles and of the mesenteric glands The solitary follicles and Peyer's patches were reported by Askanzy (1690) as distinctly swollen in one instance, the case of a 35 year old woman, a 51 year old woman who otherwise had no severe illness had an enlarged spleen In one case a grayish red, rather large thymus remnant was found In the case of an 18 year old female patient of Garre and Moses (2864) death occurred under anesthesia during a goiter operation Large hyperplastic mesenteric glands and swollen intestinal follicles and Peyer's patches, the size and number of which increased toward the lower region of the intestine, were noticed An unusually large, pale red, soft thymus was found in the mediastinum.

We shall discuss in still more detail the relatively frequent evidence, in the autopsy of Basedow patients, of persistence or hyperplasia of the thymus gland as well as the occurrence of masses of lymphatic tissue in the thyroid gland itself under the section on the Pathological Anatomy of Basedow's disease.

In addition I would like to mention one rather peculiar case of lymph-node disease observed by P J Mobius (2549) The patient was a 37 year old woman, one of whose sisters had died of Basedow's disease The patient complained of fatigue, emaciation and palpitation The examination showed only moderate enlargement of the lymph nodes After treatment with iodide of potassium prescribed by a doctor, the patient became visibly worse She became drowsy In several places an enlargement of the lymph nodes appeared The thyroid gland, heart, and eyes showed nothing abnormal After discontinuation of the iodine treatment the nodes became smaller, the nutritional condition improved, and the patient became livelier The slight effort of walking occasioned palpitation and shortness of breath Otherwise, there was only a moderate tachycardia Of the enlarged nodes finally only those on the neck remained, but the cardiac difficulty continued and a slight degree of mental weakness developed At 69 years of age the woman died of a cerebral hemorrhage The autopsy showed The

e ob-served manifestations, a poison which must be supposed to be similar to that in Basedow's disease He suggested that it was a peculiar damage to the thyroid gland

in the urine. Friedheim's (1435) 60 year old female with outspoken Basedow's disease had sugar-free urine Three hours after a sugar containing meal the urine contained 0 2% *sugar*.

Goldschmidt (1442) tested the frequency of alimentary glycosuria in Basedow's disease in a series of experiments on 17 patients, some with mild forms of the disease and some with more severe forms (see above). He found alimentary glycosuria actually much more frequently in these cases than in healthy persons, but by no means as frequent as in the aforementioned investigations. Comparative tests on the occurrence of alimentary glycosuria in neuroses, especially in traumatic neuroses and certain forms of alcoholism, led Goldschmidt to the conclusion that "in this respect Basedow's disease holds no special position as compared to the other nervous maladies". The experiments of H Strauss (1663) relate in large part to material from Senator's clinic Among 19 cases of unmistakable Basedow's disease at various stages, 3, that is 15.19%, showed a positive result An influence of the severity of the disease on the result was not discernible When he gave 6 Basedow patients 150 grams of fructose by itself he obtained a positive reaction in only one case (16 6%) A comparison of these experimental results with observations which he made on the occurrence of alimentary glycosuria in other functional disorders of the nervous system led Strauss to the conclusion that Basedow's disease, among the functional neuroses, had no unique influence on the occurrence of alimentary glycosuria. Among chronic toxic conditions, he investigated 41 cases of chronic alcoholism in whisky drinkers Three showed a positive result The number of positive results in lead poisoning was significantly larger Also, in various other toxic conditions the outcome of the experiment for evidence of alimentary glycosuria was frequently positive

Naunyn (1763) mentioned briefly that he also had found alimentary glycosuria in Basedow's disease patients much more rarely than Chvostek (only once among numerous cases)

Dienot (1709) tested 16 cases of very severe Basedow's disease, for the occurrence of alimentary glycosuria He had the patients take 150 grams of syrup every morning He determined beforehand that their urine usually was free from sugar The urine from a four or five hour period was collected and examined The result of the experiment was positive in one case only, in a woman with typical Basedow's disease signs and attacks of asystole H Stern (2238) found only 1 among 8 cases of Basedow's *disease on which he made a test for alimentary glycosuria. He gave 60 to 100 grams* of pure fructose on an empty stomach In the one positive case glycosuria was produced by the administration of 75 grams of fructose In several urine specimens 3.37 grams of sugar were excreted, that was 4.5% of the sugar taken This was by no means one of the especially severe cases, it improved considerably under treatment, while the symptoms continued in the negative cases, notwithstanding like treatment

J A Hirschl (2192) tested 20 cases of Basedow's disease from the psychiatric clinic in Vienna for the occurrence of alimentary glycosuria and could show it in 6, that is, in 30%, of the cases These 6 cases, in which the assimilation limit for fructose was considerably lowered all belong among the more severe ones, 3 cases were complicated by psychoses In 4 cases, the development of the symptom complex pro-

again become acute In the case of a 25 year old woman the disease had been present for several years; but it had reached its full development only during the last half year

can thus be determined even though the urine contains only 0 1% of fructose and the Fehling's test no longer shows a positive result.

The chief cause for variations in the results of the experiments on the *frequency of alimentary glycosuria in Basedow's disease* is probably not so much by way of the severity of the symptom complex alone but rather because cases which are progressing actively have a tendency toward glycosuria (v. Noorden, Hirschl). For instance, fresh cases with a relatively rapid development of the symptom complex, and cases with a recent relapse of a long-standing illness, as well as those which advance with the pattern of a severe poisoning, show a tendency to an abnormal decrease in the assimilation threshold for fructose.

Fr Kraus and H Ludwig (984) were the first to attempt in a systematic way to solve the problem of whether an increased alimentary glycosuria is a frequent sign in Basedow's disease In 4 out of 6 Basedow patients the two investigators were able to show definite alimentary glycosuria A 13 year old girl with typical signs of the disease, after taking 150 grams of chemically pure fructose, excreted 25 46 grams of sugar, that is 16 9% of the amount of sugar taken, and the glycosuria continued for 18 hours As a rule, however, the sugar excretion with about the same intake is much less A 50 year old woman with *pronounced Basedow's disease* excreted, in a test, only 0 14% of the sugar intake In other cases the sugar excretion amounted to 0 2% to 0 4% of the sugar intake

Soon afterward, F Chvostek (1030) reported 8 other cases of Basedow's disease of which 5 showed the presence of an increased alimentary glycosuria. The cases were typical, fully developed, but not especially severe forms of the disease The volume

without the occurrence of noticeable changes in the other symptoms, may fluctuate within rather wide limits If we combine the experimental series of the two observers mentioned above, who both refer to patients at the Vienna clinic, 9 positive results *are shown among 14 Basedow patients, that is 64 28% It must also be especially emphasized* that in tachycardia from other causes, as well as in functional disorders of the nervous system[1] an increased alimentary glycosuria is not found with the frequency and intensity that is seen in patients with Basedow's disease

v. Noorden (1484) confirmed the observation that, in the case of a person with Basedow's disease, alimentary glycosuria can be produced relatively easily by giving a rapidly assimilated carbohydrate, especially by fructose Zuelzer (1258) reported 2 cases of Basedow's disease in which after an intake of 150 grams of dextrose sugar-free urine was passed, while another patient after 100 grams of lactose had sugar

[1] Chvostek investigated 3 hysterical cases, 4 patients with tetany, 3 cases of severe neurasthenia, 4 individuals with chorea, 2 epileptics, 2 cases of *paralysis agitans*, and 3 with psychoses No variations in the sugar excretion as compared to normal persons could be discovered in any of these cases.

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can thus be determined even though the urine contains only 0.1% of fructose and the Fehling's test no longer shows a positive result.

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of excreted sugar fluctuated a good deal while a like quantity of sugar was being taken It was between 12 77 grams and 0 38 grams that is, 8 5% and 0 25% of the sugar intake In the same individual the sugar excretion, under like experimental conditions, and without the occurrence of noticeable changes in the other symptoms, may fluctuate within rather wide limits If we combine the experimental series of the two observers mentioned above, who both refer to patients at the Vienna clinic, 9 positive results are shown among 14 Basedow patients, that is 64 28% It must also be especially emphasized that in tachycardia from other causes, as well as in functional disorders of the nervous system[1] an increased alimentary glycosuria is not found with the frequency and intensity that is seen in patients with Basedow's disease.

Scholz (1377), a student of Kraus, was able, in the case of a 29 year old female Basedow patient who served him for the metabolism experiment, (see §223 above) to determine alimentary glycosuria after administering 100 grams of fructose

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§232. The occurrence of *diabetes mellitus* in Basedow's disease is of much greater significance. It is known that the evidence of sugar in the urine is, by itself, not sufficient for the diagnosis of real diabetes It must be shown that the sugar excretion exists independently from the sugar intake and that it is permanent, or at least that it extends over a long period. Accessory signs are then added: glycosuria, increased diuresis, increased thirst, and evidence of debility. Since the latter sign may also occur in Basedow's disease without glycosuria, greater weight must be laid on the evidence of acetone and acetoacetic acid in the urine. The positive result of Gerhard's ferric-chloride reaction is, then, decisive for the demonstration of real diabetes This evidence is probably given in a few of the cases described in the pertinent literature. Still it cannot be doubted that true *diabetes mellitus* was present in the great majority of these cases It was usually a severe form of diabetes The combination of the two diseases must always be considered a serious complication, since both, in their developed forms, result in a consumption of bodily strength It must also be realized here that diabetes makes difficult or impossible many of the most important dietetic measures for improvement or cure of Basedow's disease Many of the cases in which Basedow's disease occurred together with *diabetes mellitus* ended in death.

In 37 of 56 cases in which Basedow's disease was complicated by a mild or severe form of diabetes data are given concerning the course of the latter; 22 of these ended fatally, 7 in *coma diabeticum*, in several, death resulted from exhaustion, 2 patients died of tuberculosis, 1 from pneumonia, in others the cause of death is not stated

In the majority of cases diabetes followed a Basedow's disease which had been present for some time, in a series of cases the two diseases seem to have developed simultaneously, in a few it is evident that diabetes came first. Since the patients often overlook early stages and are inclined to date the beginning of their disease from the appearance of more conspicuous symptoms, the cases can not always be classified with certainty as belonging to one category or the other

Among 40 cases in which available data permit some judgment concerning this question, 26 started with Basedow's disease In many, an interval of several years occurred between the first appearance of the two diseases In 5 cases the signs of diabetes first appeared when the Basedow's disease had nearly run its course

Kleinwachter (1049) observed a 23 year old girl who four years previously developed severe Basedow's disease following an abortion There was loss of hair on head and pubic region, marked regression of the breasts, and atrophy of the right ovary (see §188) When the Basedow's disease was undergoing improvement, polydipsia and polyuria occurred and the urine test showed 1% of sugar.

H Mackenzie (2537) in a general way expressed his experience in regard to the frequency of alimentary glycosuria in Basedow's disease by saying "*it was very easy to produce glycosuria artificially by the administration of glucose*".

§231. Spontaneous temporary glycosuria has sometimes been observed in Basedow's disease It would probably be found much more frequently if sufficiently delicate tests would be applied repeatedly for the presence of sugar. K Alt (2602), in 11 of 12 Basedow cases examined within two years could determine reducing substances in the urine after a relatively carbohydrate-poor diet Following a dose of 80 grams of lactose, glycosuria appeared

The number of cases found in pertinent literature concerning spontaneous temporary glycosuria in Basedow's disease is not large. Many cases which simply mention the presence of sugar in the urine may be counted in this category.

In 2 of the 32 cases collected by A Hill Griffith (588) only a trace of sugar was found in the urine in one case, some quantity in the other In one case of typical Basedow's disease a 28 year old woman presented before the Ophthalmological Society in London, it was mentioned that sugar was discovered in the urine. Among 6 cases of Basedow's disease described by Drummond (702), sugar was found in the urine of 2, an 18 year old girl and a 50 year old woman who displayed great excitement, one suffered from a manic delirium Both cases ended fatally Burton (752) in the case of a 34 year old male Basedow's disease patient found glycosuria which disappeared after a week Runeberg (1004) found a transitory glycosuria in the case of a male. Among four sisters, all suffering from Basedow's disease, D R Brower (1699) could demonstrate sugar in the urine of two A longer-lasting transitory glycosuria was demonstrated only twice among Kocher's (2197) cases, only in a few other cases did sugar appear in the urine temporarily after a sugar-rich diet In one case sugar had been present in amounts up to 2% in the urine in the first year of the disease At the time of the observation, however, it could no longer be found The 3 cases with longer lasting glycosuria were men H Stern discovered the presence of sugar in the urine in a 41 year old Negress who had a moderately severe form of Basedow's disease for three years Later tests showed no more sugar notwithstanding the continuation of a carbohydrate-rich diet In a case reported from the Senator's clinic by Rauchwerger (2566), a 27 year old female patient whose first signs of Basedow's disease had appeared five years before, a relapse of the disease had occurred after a delivery two years before There was polydipsia, polyuria, 0 3% sugar were found in the urine In repeated later examinations the urine was found free from sugar.

C Lewin (2531) described the case of a 32 year old woman suffering from hysteria, who seemed to him undoubtedly an example of spontaneous glycosuria in Basedow's disease There was a hereditary tendency toward diabetes No sugar was found in the first examination, therefore the usual diet with much carbohydrate was continued An examination five days later showed 0 5% sugar After that the sugar content fluctuated between 0.25% and 0 75% On many days no sugar at all could be found The diet was not altered, carbohydrate intake could not influence the appearance or disappearance of the sugar excretion

Naunyn (1763) stated that he had never found a spontaneous glycosuria among the numerous Basedow's disease cases at the Strassburg Clinic.

about six years hunger and thirst increased in association with polyuria The urine contained 4 45% sugar and acetic acid A strict diet reduced the sugar loss considerably, but not for long Basedow's disease continued with a fluctuating course

H Köster (1866) reported a woman of 55 who had Basedow's disease for five years and had complained for a year of unquenchable thirst and great hunger She was extremely emaciated Her urine contained 5 7% sugar, 0 03% albumen, and gave a definite acetone reaction Suitable treatment produced temporary improvement The woman died soon afterward

A woman of 53 whose history Budde (879) reports, at 50 years of age had had attacks of burning heat sensations over the entire body, congestion in the skin, itching, and palpitation The rest of the Basedow's disease signs followed Later urticaria over the whole body for several months recurred About two years after the development of the Basedow's disease severe diabetes occurred soon leading to death in coma

A 34 year old woman observed by Barnes (805) had no hereditary tendency At 30 years of age she noticed palpitation and unusual fatigue when doing her house work Increased hunger and thirst came two and one half years later The patient passed an excessive amount of urine and became emaciated In one and one half years she lost almost all of her hair (see §207) At the time of the examination the signs of both diseases were recognized Despite suitable treatment she became weaker and died of exhaustion

Lannois (1600) described a case of chronic Basedow's disease complicated by severe diabetes about three years before death A woman of 52 without a hereditary tendency had a goiter from early youth Ten years earlier it had begun to grow rapidly and six years earlier the eyes protruded distinctly She had never complained of palpitation Four years earlier, after great excitement during the burning of her house, no basic changes occurred in the signs of the Basedow's disease But the woman developed polydipsia, polyuria and weakness accompanied by voluminous perspiration The urine contained 2 75%, later 4 5% sugar and had a strong acetone odor Initial improvement was followed by progressive deterioration which led to death from exhaustion There was a small lesion in the *corpus striatum*, the pancreas was large, soft, and weighed 130 grams

A woman, 43, reported by S West (656), had Basedow's disease for 2 years The thyroid gland was predominantly enlarged on the right side, there was a protrusion of the right eyeball For half a year she had complained of thirst and for two months of diarrhea and nausea Sugar was found in the urine Death came suddenly after temporary improvement

A woman of 38 with hereditary tendency and nervous predisposition was reported by Pitres (1632) The symptom complex of Basedow's disease developed rather rapidly About one year later thirst and polyuria appeared The urine was not examined at that time Later a strong acetone odor became noticeable and the urine examination showed 5% sugar Death in coma followed

Lauder Brunton (329) reported a 43 year old servant girl who became ill with a typical Basedow's disease after she had been grazed by a heavy object which fell from a window One year later she developed diabetes and died

A highly instructive case was mentioned by Fr Muller (2718) at the Congress for Internal Medicine in Munich For a few weeks he gave thyroid-gland tablets to a woman, who had a seemingly not very severe case of Basedow's disease Recrudescence of Basedow's disease signs was associated with a small amount of sugar in the urine, then larger amounts Although the tablets were immediately discontinued the sugar excretion continued A few months later death occurred during *coma diabeticum*

A woman of 32 with no hereditary tendency was reported by Hartmann (408) Typical Basedow's disease developed in her twenty-first year. Improvement followed after half a year The palpitation ceased and the general condition was satisfactory. During the first pregnancy, in her thirtieth year, greatly increased hunger and thirst

emaciation, debility and death soon followed

Morris Manges (2098) saw a diabetic woman of 44 who previously had had Basedow's disease Together with several other signs there was a thyroid enlargement, and pigmented spots appeared on the skin. A severe diabetes was found. The pigmentation increased still more during the interval of observation The woman died soon afterward Atrophy of the pancreas was found, together with characteristic changes in the thyroid gland (see Pathological Anatomy)

Pfibram (2727) briefly mentioned a case of severe Basedow's disease affecting one of three sisters, all of whom were afflicted by it She later developed a severe diabetes from which she finally died long after the signs of Basedow's disease had disappeared.

A 40 year old school principal, whom Salomon (2432) observed, had gone through a definite course of Basedow's disease in his twenty-ninth year After a year of electrical treatment and a sojourn in the Harz mountains the visible signs were nearly gone Only a slight thyroid enlargement and a tachycardia remained In the last four months the man became nervous and emaciated Sugar was discovered in the urine Salomon found, besides a moderate enlargement of the lateral lobes of the thyroid gland, slight irregularity of heart action and tachycardia of 110 to 120 There were no Basedow's disease signs except a considerable increase in the oxidation processes (see §223 above) Strict diet reduced the sugar to a trace as shown by ferric chloride reaction After a few days, however, in spite of strict diet, sugar amounting to between 5 2 grams and 5 7 grams per day appeared, and acetone in the amount of 0 89 grams The patient failed rapidly and died five months after a temporary recovery

Souques and Marinesco (1660) described a case in which twelve or thirteen years intervened between the manifestations of the two diseases A woman of 41 had a hereditary nervous tendency on both sides When she was 7 years of age she had collapsed after a great fright and had lost consciousness This episode was followed by a paraplegia which lasted for one year, palpitation never had ceased since that time At the end of her twentieth year the pattern of a severe Basedow's disease accompanied attacks of angina pectoris and cardiac arhythmia appeared Two pregnancies made the condition worse More than half a year earlier the signs of a severe diabetes

A woman of 44, reported by Wilks, had palpitation for a long period of time, and the complete symptom complex of Basedow's disease for about twelve years Nine years later diabetes occurred and the goiter was reduced

Hannemann's (1319) 31 year old female patient had typical Basedow's disease for nine years Two years previously the urine had still been free from sugar Suddenly polydipsia and polyuria appeared There was great emaciation in spite of a good appetite The urine had a strong acetone odor, it contained 1 8% sugar and acetic acid. Soon after the appearance of the diabetes death occurred in coma.

In the case of a 54 year old woman reported by Bettman (1406) a typical Basedow's disease followed the cessation of the menses in her forty-eighth year After

betes is mentioned Pavy (1631) a girl of 20 and a woman of 60, Lewin (777) one case, Pribram (1368) one case with lethal outcome, Murray (1625 and 2213) 3 cases (in one acromegaly was also present), Henrot (Dienot 1709) likewise, in combination with acromegaly, Berg (1816) a woman of 44 with skin pigmentation, and Otsuka (2557) 4 cases from Japan

Recorded in the pertinent literature: 8 cases in which the development of the two diseases seems to have taken place simultaneously.

A girl of 18, observed by Dumontpallier (225), had amenorrhea followed by typical Basedow's disease Soon afterward polyphagia, polyuria, and emaciation occurred Urine contained sugar up to 6% Improvement followed the beginning of treatment, but the patient soon died of pneumonia

A woman of 24 is reported by Budde (879) She had developed palpitations in her nineteenth year, became nervous, and had attacks of heat sensations and perspiration over the entire body Later the thyroid gland became enlarged and exophthalmia developed At about this time thirst and polyuria occurred Sugar in moderate amounts was found in the urine With suitable diet the urine sugar disappeared; but polydipsia and polyuria and the other signs of Basedow's disease did not improve

Gauthier (1104) reported a woman of 38, who had a severe Basedow's disease complicated by a slight paresis of the extremities, paralysis of all of the external branches of the left *N oculomotorius* (see §127), polyuria, and glycosuria with up to 4% sugar After temporary improvement the patient died suddenly

A 40 year old woman whose father was a diabetic was reported by Lancereaux (1336) He found the typical signs of Basedow's disease and of diabetes The diabetes had *been present for about one year and was characterized by thirst, polyuria, and* polyphagia A rather large amount of sugar was discovered in the urine Then the signs of acromegaly appeared (see §220 above)

E Grawitz (1579) reported a girl of 22 whose mother had died of a mental disease, and who was "very nervous" The disease began about six months previously with attacks of anxiety and palpitation A tremor arose in all the limbs There were also polyphagia, polydipsia, and polyuria At about this time the eyeballs began to protrude noticeably, and the patient became run down On examination all the typical signs of Basedow's disease were found except perspiration Furthermore, there was 4 5% sugar in a urine with a total volume of 3600 cc Acetone and acetic acid were never found in the urine but the sugar excretion continued in the decreasing amounts of 0 5 to 2% No change occurred in the Basedow's disease

A woman of 52 whom Boinet (1695) studied had polydipsia after a violent emotional disturbance Enormous amounts of urine were voided At the same time the patient complained of palpitation, shortness of breath, sensations of heat, and sweating Six months after the emotional excitement all the signs of Basedow's disease and of diabetes could be demonstrated During 24 hour intervals first 200 grams, then, later, 400 grams of sugar were excreted

Osterwald (1768) reported the case history of a girl of 18 who came from a healthy *family and was well herself About twelve weeks before the beginning of the medical* observation the patient noticed a gradually increasing enlargement of the neck and an increasing sensation of thirst, as well as greater urine output Sometimes she had sensations of heat over the whole body and profuse sweating There was a pulse rate of 88 to 180, a moderately large pulsating goiter, a fine tremor of the fingers, and much sugar in the urine (an average of 6 25%) Pronounced exophthalmia and lid signs were absent Suitable treatment resulted in improvement

A mild form of diabetes was found by Ballet (535) in the case of a woman of 37 who had suffered from typical Basedow's disease for two years For three or four months she had complained of thirst and polyuria. Repeated tests established small quantities of sugar in the urine (0 83 grams per liter). Specific gravity of the urine was 1 018

Osterwald (1768) reported a 40 year old female patient from the Göttingen Clinic. She had had Basedow's disease for twenty years and had been restored to health in Pyrmont After one and one half years she again developed Basedow's disease and went to Pyrmont for cure After a stay of three weeks she suddenly noticed unusual thirst, two months later sugar was found in the urine, 4% in an average of four samples The signs of Basedow's disease had already improved Suitable diet reduced the urine sugar content to 0 75%

A woman with no hereditary tendency was observed by H Stern (2238). She developed a typical Basedow's disease after a severe nervous shock in her fifty-fourth year, and, among the others, the nervous signs were especially conspicuous. Emaciation and debility were also prominent Continued treatment with thyroid-gland preparations resulted in almost complete recovery except for a moderate tachycardia. Three years after the onset of the first disease a severe relapse occurred, and together with this symptoms of diabetes, polydipsia, polyuria, polyphagia, and glycosuria appeared The woman was excited and restless and entered a phase of slight mental disturbance In six weeks she lost 20 kg and vomited frequently Vascular signs over the thyroid gland were distinct Abscesses formed on both corneas, the sugar content of the urine fluctuated between 0 15% and 1 15%. The acetone test gave a more or less distinct reaction After progressive loss of strength the patient died five months after the beginning of the relapse

A number of cases were reported in which diabetes complicated an existing Basedow's disease But no exact information is available concerning the time of the occurrence of diabetes

O'Neill's (412) 42 year old patient had a definite Basedow's disease for about twelve years Furthermore, there were signs of a rather severe diabetes Suitable treatment produced, at first, an improvement of both diseases and later again an exacerbation. Death occurred with signs of bronchitis and hemoptysis

A 40 year old man, observed by Fischer (465) fell ill of typical Basedow's disease Later he complained of thirst, polyuria and debility Sugar was found in the urine. Potain (498) mentioned a case of Basedow's disease involving a man who later displayed the signs of diabetes

Cohen (1041) and Mannheim (1222) gave the case history of a woman of 42 years of age who had pronounced signs of Basedow's disease for five years. Later, she complained of thirst and polyuria, became emaciated and died Her urine contained 2 9% sugar

Roper (1911) reported a 27 year old woman who had Basedow's disease for six or seven years Later, sugar was discovered by chance in the urine The amount varied

tendency. Basedow's disease followed influenza, and became fully developed after a delivery A sugar content of 3% was subsequently discovered in the urine After a sojourn in the country sugar excretion was reduced to 0 4% or 0 5%, sometimes still less, while the Basedow's disease continued.

In the following cases only the concurrent presence of Basedow's disease and dia-

months, supposedly from a fall on the back of the head, there also was a Basedow's disease There was no palpable goiter among the signs The urine contained 0 3% sugar, much acetone, and acetoacetic acid Suitable treatment soon caused the sugar to disappear from the urine

A few statistical data give us an approximate estimate of the frequency of appearance of Basedow's disease combined with diabetes.

A Hill Griffith (658) mentioned twice the occurrence of sugar in the urine among 32 cases Perhaps, however, this was only temporary glycosuria (see §231 above) S West (686) found one case with diabetes among 38 Basedow patients (see above), Lewin (777) 1 among 27, Mannheim (1222) 1 among 47, Roper (1911) 3 among 30 cases in which the urine was examined (whether in all of these 3 cases real diabetes was present is not certain in 2 it is probable) Stern (2239) observed, among 10 cases of Basedow's disease, 1 in which it was combined with real diabetes (see above), and 1 with spontaneous glycosuria Rauchwerger (2566) and Morse (2665) noted, among 22 Basedow's disease patients, 1 with diabetes and 1 with a spontaneous glycosuria W G Thompson (2773) mentioned 3 among his 80 cases and Frank Billings (2806) among 61, 1 in which Basedow's disease was associated with diabetes More exact data are lacking Kocher (2197) found, among his numerous cases, none with a combination with real diabetes His observation concerning transitory and alimentary glycosuria has been considered above (§231)

If we permit ourselves to draw a conclusion from the given data, which, to be sure, are not numerous enough, considering the negative results in Kocher's material, the frequency of diabetes in Basedow's disease would amount to about 3%

§233. It is now in order to discuss the problem of whether a combination of Basedow's disease with diabetes is a matter of chance or whether a closer relationship exists

Undoubtedly, there are cases which must be assumed to be due to chance. As such, especially, must be counted cases in which the diabetes arose only after the Basedow's disease had largely disappeared (see §232), and probably also those in which diabetes was present previously Among these, a pronounced predisposition to Basedow's disease seems to play a role as shown by Grube's case (see above)

First of all, one fact should not be overlooked which speaks in favor of a closer connection between the two diseases While Basedow's disease in particular occurs much more frequently in the female sex and most frequently in the younger years, diabetes on the contrary is conspicuously more frequent in men, occurring chiefly in the advanced years of life (most frequently between the fortieth and sixtieth year) We find that the female sex is much more frequently represented in the combination of Basedow's disease with diabetes, the ratio with respect to the two sexes approximately corresponds to Basedow morbidity in general.

Elliot's (2488) 54 year old patient had always been nervous and had noticed an enlargement of his neck five years before. Gradually the other signs of Basedow's disease appeared Only exophthalmia and lid signs were absent. At about this time the patient noticed that he voided an unusually large amount of urine and that he was very thirsty Occasionally, he also felt a voracious appetite. The pulse rate was 126, and the heart action irregular There were pronounced arteriosclerosis and insufficiency and stenosis of the mitral valves The patient was emaciated In the urine albumin and 3% of sugar was found at the first examination In the eyes signs of a *retinitis albumenurica* with numerous hemorrhages in the retina were noticed Suitable treatment resulted in improvement No information is given concerning the further course of this illness

In 6 known cases diabetes was present before the appearance of the Basedow's disease.

In Hartmann's (407) case there was evidently a short interval between the appearance of the two diseases A woman of 32 without a hereditary tendency had a small goiter since her eighteenth year Over a period of two years it had grown noticeably At this time her eyes, which had always been somewhat staring, protruded still more For three years she had complained of thirst, polyuria, loss of strength and progressive emaciation in spite of strong sensations of hunger. For nine months she had attacks of palpitation, nausea, and weakness The pulse rate reached 100 to 140 beats per minute The urine showed an average of 5% of sugar Suitable diet produced improvement followed by an increase of the greatly reduced weight, but the sugar did not disappear from the urine and its volume always amounted to over 4%

A case described by M Schmidt (1074) was a man of 32 whose symptoms began with thirst and fatigue This was followed by palpitation and exophthalmia The patient sweated profusely and had a tremor of the whole body A goiter was absent Repeated examinations demonstrated 2% to 6% of sugar in the urine. In the course of the observation no great improvement took place

Grube (1317) observed a woman of 50 who had had diabetes for some time Frightened when being told that her urine contained 9% sugar, she developed strong cardiac palpitation and an enlargement of the thyroid gland A suitable diet improved [illegible] 'hen these had reached [illegible] About six weeks after [illegible] death occurred Dienot (1709) reported a case observed by Lepine A woman of 63, nervous but without hereditary tendency, experienced a great fright, followed by a year of continuous thirst and polyuria This woman was pale and emaciated, and her urine contained much sugar Seven weeks after the first observation high degree tachycardia arose without special cause, moderate tremor and a right-sided goiter were discovered Exophthalmia seems not to have appeared In the further course there was remission of the Basedow's disease but not of diabetes Ten weeks later the patient died of pulmonary tuberculosis

Runge (2228) reported 2 cases in which the symptoms of Basedow's disease were combined with diabetes A man of 60 had had a goiter since youth and, for a long time, had suffered from thirst and polyuria Within half a year the signs of Basedow's disease had gradually developed In the urine, 5% of sugar was found A woman of 26 who previously had been chlorotic, had suffered for 3 years from fatigue, thirst, and sensations of hunger Then the presence of diabetes was demonstrated For two

erated The patient developed tremor of the arms, hot flushes, outbreaks of sweating, sleeplessness, and a voluminous urine output containing albumen and sugar

v Notthaft (1764) reported a similar but much more severe case Because of obesity a healthy man took English thyroid tablets of 0 3 gram without a doctor's orders In the course of five weeks he consumed nearly 1000 of these At the end of the third week signs of thyroidism appeared and increased to such a point that the patient went

already considered above Fr Müller's (2718) probably exceptional case (§232). In the course of an average Basedow's disease the use of thyroid tablets was followed by a severe diabetes which ended fatally during coma

Even with mild symptoms of thyroidism, sugar is often found in the urine James

tinuance of the medication the sugar disappeared from the urine

The following year, Ewald (1304) gave an interesting account of a glycosuria following use of thyroid tablets in the case of a myxedematous female patient Three weeks after the administration of the tablets unquenchable thirst occurred, and 4% of sugar in the urine was demonstrated After discontinuance of medication the sugar decreased to 2 8%. Despite a suitable diet it increased again to 6% three days after the tablets were resumed With cessation of the thyroid-gland intake the sugar disappeared after eleven days So the fluctuations went on for two months with taking or withholding of the tablets Notwithstanding a strict diet the sugar content in the urine remained, after months it still amounted to between $^3/_4$% and 1% No symptoms were associated with the glycosuria

Soon afterward Dennig (1292) made the observation on himself, and on a strong man with lupus on his cheeks, that the use of thyroid tablets was accompanied by decrease in weight, increased nitrogen excretion, and sugar in the urine A short time after discontinuance of the tablets the sugar disappeared completely from the urine Increased thirst and polyuria did not occur during this experiment

v Noorden made the surprising report that, among 17 obese persons, sugar was found in the urine of 5 after continued use of thyroid tablets A 45 year old obese lady with hereditary predisposition for diabetes had traces of grape sugar in the urine after she took 9 tablets in three days This disappeared immediately after the discontinuance of the tablets One or two weeks later, after 75 grams of grape sugar was *given separately, in the morning, glycosuria was again evident*

Senator (1501) saw glycosuria arise under thyroid treatment for Basedow's disease A mild transient glycosuria was observed by Hennig (1448) in the case of an obese woman receiving iodothyrin Friedheim (1435) studied a 20 year old man with hereditary predisposition This patient, who customarily drank much beer, had a temporary mild glycosuria after taking 330 thyroid tablets of 0 2 grams each within 22 days to cure obesity In the case of a man of about 30 with combined symptoms of myxedema and Basedow's disease (see §221), reported by Osler, (1893) thyroid gland therapy led to polyuria, glycosuria, albuminuria and emaciation

With so extensive a use of thyroid preparations for goiter, obesity, and other maladies the occurrence of glycosuria still must be called a rare occurrence. Among his large observation group collected with this symptom in view, v Bruns (1411) has observed glycosuria only quite rarely Stabel (1510) found occasional sugar in

Out of 46 cases in which sex is stated, 39 were female and only 7 male. Among 6 cases with preceding diabetes, 2 patients were males

In regard to age the incidence approaches what we find for diabetes. Basedow's disease morbidity figures, especially among women, are highest between the twentieth and fortieth year of life Of the cases complicated with the diabetes not even 50% (in women it is 45 9%) fall within this age group In the following twenty years this morbidity rate far outstrips that of uncomplicated Basedow's disease, and amounts to 51 35% Only 1 of the 4 men whose age is noted was under 40, 3 were between 40 and 61. In diabetes, more than a third of all the cases are in the age group from 40 to 60.

We also find a factor common to both diseases in regard to the etiology. This factor is the unquestionably important role which violent mental influences play in the production of the one or the other Bonnet's case serves as a significant indication (see above). In both diseases, great emotional excitement may not infrequently lead to an exacerbation of all disease signs or bring certain signs to full development for the first time A further indication of a relationship is represented by the occurrence of one or the other disease in various members of the same family

Especially interesting in this connection are the results reported by Allan Reeve Manby (848) 1 The father of a patient with Basedow's disease died in his seventieth year of diabetes and a brother of the patient also had diabetes 2 The sister of a woman who died from severe Basedow's disease with maniacal attacks died of diabetes and a brother of this patient lost two children from acute diabetes 3 Among three sisters, two died of acute diabetes in their ninth and tenth year respectively The sister fifteen years later, in her twenty-third year, showed signs of Basedow's disease

In the case described by Lancereaux (1336) the father of a woman of 60 with signs of Basedow's disease and of diabetes (see above) fell ill at the same time with diabetes

Přibram (1368) mentioned that the father of a patient with Basedow's disease and diabetes (see above) had died of diabetes Members of the patient's family suffered from severe neuroses

Schmey (1648) reports that the 64 year old father and the 37 year old sister of a patient with Basedow's disease and a mental disorder suffered from diabetes

The mother of a 50 year old patient, reported by Dienot (1709), was very nervous and died of diabetes, the father had "pronounced exophthalmia" Four sons of the patient were said to have a similar disorder In one of these, an 11 year old boy, typical Basedow's disease was recognized

Of great importance for judging the relationship between diabetes and Basedow's disease is the fact that the intake of thyroid-gland preparations can produce glycosuria.

Béclère (1172) first reported such an observation A 31 year old man with signs of myxedema consumed large quantities of sheep thyroid gland—92 grams in the course of eleven days The pulse became very rapid and irregular and the breathing accel-

crated. The patient developed tremor of the arms, hot flushes, outbreaks of sweating, sleeplessness, and a voluminous urine output containing albumen and sugar

v. Notthaft (1764) reported a similar but much more severe case Because of obesity a healthy man took English thyroid tablets of 0 3 gram without a doctor's orders In the course of five weeks he consumed nearly 1000 of these At the end of the third week signs of thyroidism appeared and increased to such a point that the patient went to a doctor for treatment The entire symptom complex of Basedow's disease was evident. The somewhat increased urine output showed a rather considerable amount of sugar (1%) but no acetone The symptoms soon improved after discontinuance of the medication After two weeks the sugar had disappeared from the urine We have already considered above Fr Muller's (2718) probably exceptional case (§232) In the course of an average Basedow's disease the use of thyroid tablets was followed by a severe diabetes which ended fatally during coma

Even with mild symptoms of thyroidism, sugar is often found in the urine James Dale (1189) reports a man suffering from psoriasis who had taken thyroid tablets for a long time, after a week of general depression he had palpitation and tachycardia The urine contained sugar but the volume was diminished Nine days after discontinuance of the medication the sugar disappeared from the urine

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the urine only once among 35 goiter sufferers treated with thyroid preparations. Leichtenstern, as Becker (1271) reports, had administered thyroid substance in 162 cases of obesity and other conditions With careful dosage and exact control he never

[illegible] sugar, but no other signs of thyroidism appeared either Becker had assured himself that these same tablets were quite efficacious in other cases Even among Basedow's disease patients the effects of thyroid tablets have been harmless in a number of cases, and were not associated with occurrence of sugar in the urine (see Therapy). Goldschmidt (1442) reported 3 cases of Basedow's disease in which, after previous long-continued use of thyroid tablets, the test for alimentary glycosuria was negative.

Bettman (1535) tested the influence of thyroid preparations on the occurrence of glycosuria on 20 persons, including 5 men and 5 women whose urine, according to a preliminary examination had been free from sugar. These were all persons with an average state of nutrition and between the ages of 15 and 20 The test substances used were partly Doepper's thyroidin tablets, partly iodothyrin in powder form The constant effects were an elevation of the pulse rate and an increase in urine volume. Subjective cardiac difficulties, tremor, disturbance of sleep, and nervous excitement were never observed. The test subjects were given either thyroidin or iodothyrin in increasing doses, during a seven-day period, but never more than 3 x 3 tablets, or 3 x 0.5 gram of iodothyrin. On the eighth day they were given 100 grams of fructose with the last dose In 11 of the 20 persons upon whom the experiment was made, alimentary glycosuria appeared, that is, in 55% of the cases. The polarization tests in no case gave a higher value than 0.6% for fructose After four or five hours most of the sugar had disappeared from the urine. In all positive cases a dose of 100 grams of fructose was again given eight days after the end of the experiment, none of these control tests showed glycosuria Similar experiments have been made by H. Strauss (1663) He gave 4 English thyroid tablets daily for five to twenty-five days to experimental subjects whose urine contained no sugar after an oral dose of 100 grams of fructose After eight days, 2 additional tablets were given; a routine test was made for alimentary glycosuria. When the test showed positive, administration of the tablets was discontinued and after a time another test was made without any thyroid tablets but with an oral dose of 100 grams of fructose Glycosuria was attributed to the thyroid gland administration only when this experiment showed a negative result. Only 3 of 15 persons, who were used for such experiments, showed a positive result. In the cases of 2 patients, one a man of 40 with a focal syphilitic affection of the brain and the other a man of 49 with bronchitis it had been determined by preliminary experiment that even a relatively small stimulus was sufficient to produce

spontaneous glycosuria in the urine In each of these cases Strauss observed a spontaneous glycosuria after administering thyroid tablets Sugar appeared in the urine when the patient took no fructose except that of the usual carbohydrates of the diet. Glycosuria, in both cases, lasted a number of days beyond the period of use of the tablets. In 1 case, that of a schnapps drinker with symptoms of a beginning delirium, Strauss could show that the acetone which produced the alimentary glycosuria during acute alcohol poisoning had a stronger action than 24 thyroid tablets which the man took within eight days A test to produce glycosuria by this dosage turned out to be negative. Mawin (1621), at Strauss's instigation, re-examined the influence of thyroid gland preparations upon the occurrence of glycosuria, with special attention to Bettman's experimental setup since he considered it the reason for the difference in the results of Bettman's and Strauss's experiments For a long time Strauss only gave small doses of thyroid He chose only persons for the experiment who did not show the slightest disposition toward alimentary glycosuria, 20 men and 3 women between the ages of 15 and 51 He used the English thyroid tablets of 0 3 grams These, according to chemical analysis, have a content of organically combined iodine five times greater than the Doepper tablets. A positive result was obtained only in the case of 2 women who took 48 tablets within a period of 8 days The test for glycosuria was repeated in the cases of these patients, 8 days after discontinuance of the tablets One then gave a negative and the other a positive result

For the purpose of clarifying the relationship between the thyroid gland and glycosuria, experiments have also been made on animals Fr. Muller (2718, p 104) reported that Kulz recognized such a relationship Kulz's experimental studies on this subject were broken off by his death Medinger (Inaugural dissertation, Greifswald, 1895) found sugar in the urine of a dog which had been fed thyroid glands Georgiewsky (1575) made exact metabolism experiments on dogs which he fed with thyroid preparations He found, besides tachycardia and tachypnoea, a slight rise in temperature, excitement, polyuria, polydipsia, polyphagia, and several times glycosuria M. Porges (2007) reported an experiment on one of the many dogs which were fed with thyroid in Blum's laboratory This dog reacted more intensively to the feeding than is usual The metabolism was determined before, during, and after the thyroid feeding. The nitrogen loss continued in greater degree afterward and a not inconsiderable glycosuria (up to 0 5%) appeared which lasted for several days after the intake of thyroid substance

If we now summarize the collected factual material, the not really uncommon occurrence of alimentary glycosuria in Basedow's disease as well as the occasional appearance of sugar in the urine of human beings

as well as of animals following the consumption of thyroid gland material, we cannot avoid the impression that a certain connection exists between the so-called *hyperthyroidism and the sugar content of the urine* Very instructive in this connection is one other observation reported by Fr Muller (2718) A woman with a large goiter, who had been treated with thyroid tablets, over a long period of time, showed a moderately severe diabetes continuing for years The urine contained 3 to 5% sugar. It could not be stated with certainty whether her urine had not contained sugar before the thyroid treatment. The interesting observation, however, is that when in recent years the goiter became reduced without further treatment, the sugar in the urine also disappeared. Even after the con*sumption of large amounts of carbohydrates* no more sugar was found in the urine Fr. Muller has added, very correctly: Cases of genuine diabetes are rare, so it seems natural to hold that the melituria is connected with the goiter On the other hand, the results before us teach that an individual predisposition plays an important part, and that the thyroid gland, at least in the majority of cases, produces glycosuria or a tendency to glycosuria only on the foundation of an already existing predisposition. Yet it seems to me that Naunyn goes a little too far when he states that the thyroid gland causes glycosuria only when latent diabetes already exists

We know that a considerable rise in the metabolism is characteristic of *Basedow's disease We have also established the probability that the thy*roid gland participates in this alteration of the metabolism to a predominant degree On the other hand, it is known that in diabetes the organism has largely lost the power to utilize carbohydrate in the normal way. The important regulatory influence of the pancreas on the oxidation of sugar in an organism is doubtless due to the fact that a peculiar internal secretion of this gland is introduced into the blood and thus, to the muscles and the liver, an indispensable agent for normal sugar metabolism. *It has* been established that certain lesions of the pancreas under certain circumstances may lead to diabetes and that certain disorders of the nervous system can also produce diabetes. The nervous system exerts an influence on sugar mobilization in the liver and on the sugar content of the blood From the results before us I consider it very probable that the alimentary or spontaneous melituria which sometimes follows the feeding with thyroid products, the alimentary glycosuria in Basedow's disease patients, and the cases of diabetes in Basedow's disease are not purely chance com*plications but are of a toxogenic nature*

One must probably assume that toxic products of the thyroid gland either influence the internal secretions of the pancreas directly or act through the mediation of the central nervous system on liver and pancreas. This much is certain: in man the diabetogenic function of the central

nervous system *is not strictly confined to the region of the experimental* lesion of the floor of the fourth ventricle, although nervous tracts in that area seem to be important in the etiology of diabetes (Naunyn) Among the few autopsies which have been made in cases of Basedow's disease with diabetes, an atrophy of the pancreas was found in only one instance, the case of Morris Manges (see §32 above) in which a severe diabetes was first discovered after the Basedow's disease was already in a stage of recovery. In the light of our present evidence it is in no way justified to regard the simultaneous occurrence of the two diseases as evidence of a bulbar localization of Basedow's disease, as was previously done by many authorities Chvostek called attention, in this connection, to the opposing behavior of the assimilation limit for fructose in Basedow's disease and in the nervous glycosurias

Lorand (2312) might have been right when he stated that the glycosuria which occasionally occurs in chlorotics, and that in pregnancy and in lactation, is to be attributed to an increased activity of the thyroid gland On the other hand, glycosuria is extremely rare in all inactivity states or states of exhaustion of the thyroid gland.

Basedow's disease and diabetes belong, according to present-day conceptions, among the diseases of internal secretion such as acromegaly, myxedema, and other metabolic disorders Eppinger, Falta, and Rudinger (2918) have come to the conclusion, from their experiments on animals, that a close connection in the nature of a mutual inhibition exists between the thyroid gland and the pancreas, such that an overproduction of the internal secretion of the thyroid produces a relative insufficiency of the pancreas (see also §223, above).

Polyuria

§234. Polyuria caused by the inability of the kidneys to produce a urine of normal concentration but without the presence of abnormal elements, is often observed in Basedow's disease

Lustig (917) measured the daily volume of urine of two patients for twelve days He found that, while the daily volume of urine in healthy persons varies rather constantly around an average of about 1000 cc, the volume of urine excreted daily by a patient with Basedow's disease shows much greater fluctuations, up to double those of the control individual, or even more He believed these fluctuations to be attributable to manifold influences of the nervous system among patients with Basedow's disease

Although one cannot even in these cases speak of a true polyuria, cases do occur in which, within 24 hours, the volume of excreted urine reaches 5 or 10 liters.

Such cases are described by Bruck (112), Pulitzer (217), Korach (435), Potain (498), Starcke (505), Renault (931), Boinet (1695), Jeunet (1740), Breuer (1944); Babini (2452) observed one incompletely developed case, and A. W. Hale White (687) has observed polyuria in one among a considerable number of his Basedow's disease cases

and Mannheim (1222) 13 times among 47 cases from the same polyclinic, 3 times symptoms of hysteria were noted at the same time but only once in a pronounced form Among 17 Basedow cases from the Zurich clinic, as reported by Ditisheim (1293), the volume of urine was considerably increased in 7. Pässler (1362) noted polyuria in only 4 among 51 polyclinic patients, all of these cases had constant sensation of thirst Revilliod (1373) mentioned polyuria twice among 11 cases, and among Kocher's (2197) numerous cases polyuria was present in 4 None of them had a polydipsia at the same time

These data show the frequency of this symptom to be 13 5%. Sometimes polydipsia is present together with polyuria.

In a case described by Budde (879), a girl of 24, the signs of Basedow's disease and diabetes developed at about the same time (see §232) Polyuria and polydipsia continued after the disappearance of the sugar

Polyuria is sometimes accompanied by other watery excretions, including profuse sweat secretion and diarrhea In Pulitzer's (217) case ptyalism was also present, and in Jeunet's (1740) case profuse diarrhea occurred together with great flow of saliva.

Polyuria can occur among the early signs of Basedow's disease and it can last sometimes for several months (Hale White 687, Renault 931, Boinet 1695). In several cases polyuria seems to be a sign of a hysterical complication of the Basedow's disease as in a case of Ballet (747), a man of 33 (see §127 above), and in Mannheim's (1222) 3 cases. The lack of concentrating ability, indicating a functional disturbance of the kidneys, seems to be caused in some manner by nervous influences (Claude, Bernard, Eckhard). In many cases slight changes in the floor of the fourth ventricle have also been found. Such an alteration of the kidney function may follow a great fright, migrane, epilepsy, states of nervous excitement In all of these states, such a change in kidney function is probably produced by transitory nervous influences as in the form of polyuria known as *diabetes insipidus*. In Basedow's disease an influence on the particular center in the floor of the fourth ventricle probably caused by toxic action must be kept in mind. Among the manifestations appearing after feeding thyroid substances, distinct increase of urine volume frequently occurs. Whether the increased urine excretion is to be considered as favorable is quite as doubtful as the possible influence of the rise in blood pressure often found in Basedow's disease (see §7 above).

Polydipsia

§235. Continued sweating and watery diarrhoea and the resulting thirst in the form of a burning sensation in the mouth and throat (see §165 above) causes many patients with Basedow's disease to drink a great deal of water. Mention has already been made of the keen, sometimes unquenchable thirst of Basedow's disease cases combined with diabetes, and of polydipsia sometimes occurring with the polyuria In isolated cases of Basedow's disease, however, this symptom is present continuously and may become very tormenting. Sometimes it occurs sporadically as in Westedt's (871) case in which the attacks occurred at intervals of three to seven weeks and lasted several hours.

Lanz (2306) observed a woman of 38 with severe Basedow's disease and polydipsia. One of my own patients, a 28 year old woman, complained of continual thirst at the height of the disease, this thirst was not associated with sweating or watery diarrhea Cohen (1031) noted polydipsia 3 times among 16 cases. Among Pässler's (1362) carefully observed polyclinic patients, 17 suffered from distressing thirst, only 4 had polyuria or polydipsia Among Kocher's (2197) numerous cases polydipsia appeared in 14 cases, in a few of them since the onset of the disease Sometimes the thirst was very distressing None of these cases showed polyuria or glycosuria

Albuminuria

§236. Albuminuria is among the rather rare signs of Basedow's disease Usually it is only mild and transitory, like so many other Basedow's disease signs, sometimes it is intermittent With the regression of the other disease signs the albumin also disappears from the urine That this albuminuria is not connected with organic alterations in the kidneys is evident from the lack of cellular elements in the urine From all this we can probably conclude that this is not a chance complication, but that albuminuria has an etiological connection with the other Basedow's disease signs and is due to a toxic injury to the kidneys

Cases belonging here have been observed by Banks (51), Hiffelsheim (121) Freidrich (191), *W Begbie (295)*, *Merklen (494)* during an acute exacerbation, by *Ballet* (535), Charcot (613), S West (686), Oppenheim (855), Westedt (873), Schenk (938), Hay (976), Gowers (1042), H Batty Shaw (2232) and Stumme (2888) A Warburton Begbie (295) mentioned temporary albuminuria as a not infrequent sign in his cases, it came usually at meal time S West found traces of albumin in 3 of his 38 Basedow patients (case 8, 11 and 20), Cohen (1031) in 3 among 51 polyclinic patients, J Russell-Reynolds (932) in 2 among 49 cases, Dienot (1709) 2 times among 16 cases H Mackenzie (2205) found albuminuria in 6 of his 52 cases, Kocher (2197) in 2 among 80 cases, and Murray (2553) 6 times among 30 of his cases in which the urine was examined Hill Griffith (658), on the contrary, could find albumin in the urine of none of his 32 cases.

According to these statistical notes albuminuria was observed in about 11% of the cases of Basedow's disease.

In severe cases of Basedow's disease with cardiac dilatation and congestive phenomena, the albuminuria is probably the sign of congested kidneys, as in Stiller's very critical case (793) which finally took a turn toward recovery, and in Roper's case (1911) which ended fatally with evidence of endocarditis and pericarditis. Passler (1362) found a good deal of albumin in the urine of one of his 51 cases, associated with hyaline and granular casts Elliot (2488) had a 54 year old male patient with Basedow's disease with pronounced arteriosclerosis, and insufficiency and stenosis of the mitral valve. The urine contained sugar and albumin as well as casts and renal epithelial cells.

Part II. The Forms of the Disease; Its Course, Incidence, Distribution; Basedow's Disease in Childhood

The Various Forms of Basedow's Disease

§237. In the description of the symptomology of Basedow's disease we have constantly reiterated the changeability of the occurrence and extent of the several signs of this disease There are only a few signs almost never absent in the typically developed and what may be called the classic form *of the disease. A single case in which all signs are found together or successively* has probably never been seen It is not the number of the signs present, but the characteristic grouping, which is conclusive for the diagnosis. There are symptom-rich forms—for the period of peak development—and symtom-poor forms of Basedow's disease

If one has the opportunity to observe one case over a long period of time, he sometimes sees the originally monotonous pattern become varied by *the appearance of various secondary signs We know that many disease* signs last for a shorter or longer time Then, without one's being able to speak of an improvement in the disease, they permanently or temporarily disappear or are displaced by others

It should not be overlooked that many cases in the literature, particularly the older portion of it, seem poor in signs and symptoms only because they were not [illegible]

One can differentiate between a complete and an incomplete form of Basedow's disease.

The first is represented by the typical or classic *morbus Basedowii.* Four cardinal signs are hardly ever absent; vasomotor disturbances, increased perspiration, characteristic mental alterations, and the peculiar metabolic anomalies Furthermore, there are usually present more or less numerous accessory signs such as the lid signs, diarrhea, skin pigmentation, etc.

As to incomplete forms of the disease only those should be so designated which lack one or more of the chief signs, as far as it is possible to follow it during its entire course, or, at least, during a long period of the illness.

Almost all cases, with the exception of some with acute course, are more or less incomplete in their development. But these will not be discussed at this point.

We know today that cases occur very frequently which lack one or the other of the chief signs, and in which only a few characteristic manifestations point to a diagnosis of an incomplete form of Basedow's disease. We should not deny that among these many a case remains uncertain or would not bear closer criticism. It can happen that the absent signs or symptoms may appear only after the disease has lasted for years, or from a special cause.

In a fatal case observed by Williamson (1523) exophthalmia and thyroid enlargement came only nine months before death, after a two and a half year illness (see also §239 below)

The concept of "symptom-rich" and "complete" is as incorrect as "symptom-poor" and "incomplete" A case can be very "symptom-rich" and yet be incomplete.

For the incomplete cases the designation "*formes frustes*" is often used in pertinent literature.

Trousseau (128) was the first to select this expression for certain forms of Basedow's disease, "the illness may be designated a *forme fruste* by the absence of goiter or exophthalmia, but I hasten to add that usually sooner or later the missing sign will be seen to appear" When one or another of the chief signs is absent the "train of secondary signs" can sustain the diagnosis of Basedow's disease Trousseau once recognized in the case of a lady from Geneva the nature of the malady from the nervous signs alone, in the absence of the typical trio, and was able to predict the development of goiter and exophthalmia which followed later

In his thesis, P. Marie (1555) drew the boundaries more narrowly: one understands by the term *forme fruste* of Basedow's disease a case in which the pathognomonic signs are more or less absent after some time, and after a progressive course from the onset.

Charcot (613) distinguished, in addition to the primary *formes frustes*, secondary rudimentary forms arising in genuine Basedow's disease which was in the process of disappearing.

P. Marie (555, p. 52) has already pointed out, quite rightly, that the term *fruste* is an unfortunate choice. The word means worn-out or weathered and is used in relation to coins. One speaks of a medaille fruste when, after long use, its stamping or elevation becomes blurred or indistinct. Such a coin can scarcely be recognized any more and cannot be repaired. All this does not apply to the forms of Basedow's disease which remain undeveloped If one wishes to use the word at all it should be done, as was stated above by adhering to the limits of Marie's definition.

§238. Charcot (815) explained, probably correctly, that tachycardia is the one sign which is never entirely absent in the course of the disease. "No tachycardia, no Basedow's disease." Ballet (535) and Rendu (565) express the same opinion. Very frequently tachycardia and palpitation are the first, or among the first, signs of the beginning disease In a few cases, this begins in combination with tremor of the hands, general nervousness, and tendency to perspire The latter signs may precede by some time, or even by several years, the development of other Basedow's disease signs (see also §266 below)

Sometimes, such cases remain permanently incomplete (see also §245 below). As we have seen (§4 above), many patients, in spite of marked tachycardia, are not troubled by palpitation and thus do not become conscious of this tachycardia These signs can escape the knowledge of the patient for a time entirely.

This was probably so in many of those cases in which the illness was said to have begun when exophthalmia and lid signs etc made their appearance Sometimes, it is merely mentioned that palpitation was absent, nothing is said concerning the presence or absence of tachycardia

It can happen that the heart action becomes quiet while the other signs continue in a pronounced form In many case histories in which heart action is called normal we read that the patient has previously suffered from palpitation, either for a limited time or continuously

A first-class example of this kind has been mentioned previously (§225) In the case of Friederich's (191) 30 year old female patient, the stormy heart action quieted down nine days after its rather sudden occurrence The pulse even went below normal, from 66 to 50 beats, while carotid pulsation, pulsating goiter, and exophthalmia were still unchanged after three months A 17 year old male observed by Th Reid (677) suffered for only a few weeks from palpitation which had begun a year before [illegible]
Under suitable treatment all the signs except exophthalmia disappeared completely An instructive case of R Stern (3060) was a patient he had had under observation for a long time This man came to the doctor's office one day with the happy news that he had had no more palpitation for several hours His pulse also had become quiet A few days earlier Stern had auscultated the pulse at 108 Now it was actually only 88 Under further observation the pulse rate remained low But now and then brief attacks of tachycardia occurred preceded by a sensation of heart stoppage The feeling of fatigue also was gone, but, aside from the slower pulse rate, all the objective signs continued in a well-developed form

Perhaps the course has been similar in other cases which showed no cardiac signs at the time of examination.

Although continuous tachycardia is characteristic for Basedow's disease (§2) yet, exceptionally, cases occur in which, with the typical development

of the other signs, tachycardia, at least for a time, is paroxysmal. Then, in the quiet intervals, the pulse scarcely goes above the physiological limits

In a few cases the palpitation becomes perceptible only some months or years after the appearance of goiter and exophthalmia. Whether an abnormally high pulse rate was present before cannot be ascertained from the data given.

Beni Barde (296) reported two highly nervous persons, one a girl and one a young woman Each had a pulsating goiter and bilateral exophthalmia No disorder of the heart was evident, and no palpitation.

In Cheadle's (331) case heart signs were absent But there was a violent readily visible carotid pulsation and a distinct thrill palpable over the goiter. Two sisters and an aunt of the patient suffered from a typical Basedow's disease.

A 46 year old female observed by Chvostek (399, 23rd case) showed signs of Basedow's disease in high degree, but she never complained of palpitation in the entire course of the disease The frequency of the heart beat fluctuated between 96 and 120

Acchiote (2252) found a 40 year old female with a pronounced tremor, exophthalmia, v Graefe's sign, and a few secondary signs, the pulse rate was 55 per minute. A more or less distinct development of the symptom complex except for the lack of the first cardinal sign is noted by Prael (67) in two cases [1] Other cases include those reported by Morrell Mackenzie (214) Chisholm (242), Jensen (358), Liddell (436), Kahler (775a, p 379), Jessen (1590), Hinshelwood (1752) a 24 year old female with unilateral eye signs, Gerard Marchant (1752), Stinzing (2021), R Witmer (2034) once among 34 cases, Guibert (2185), Adam (2253) in 1 case which seemed to be in a state of regression, and Guttman's (2380) case with only leftsided goiter and leftsided eye signs

Among my own 108 cases there are 10 in which the pulse rate was less than 90 In a few of these the disease was in a state of remission, in other cases the patients complained of palpitation despite a relatively low pulse rate which sometimes lasted for a long time, some had a previous history of cardiac difficulties

v Dush (207) found cardiac symptoms absent in 3 among 58 cases. Mooren (1759) stated that, among 58 cases, he had noted the absence of accelerated heart action 4 times In the case of a 23 year old female the only signs upon which a diagnosis of Basedow's disease was based were a left exophthalmia and a bilateral v. Graefe's sign (see §47, above)

Other cases in which disorders of the heart were absent and the eye signs drew the chief attention have been mentioned above I refer to the cases mentioned in §47, by Lang and Pringle, Snell, Bassler, Awerbach and the case of a 53 year old female observed by myself In one of the following paragraphs we shall come back to this category of incompletely developed cases (see §246 below)

§239. Together with tachycardia and palpitation, goiter belongs among the essential distinguishing signs of Basedow's disease. This sign, however, is absent from a number of cases under circumstances the most important of which are mentioned above (§20). It must not be forgotten that certain pathological alterations in the blood supply and in the histological structure of the glands, which we shall come to know better later and not the

[1] There is only the remark: no statements of the patient refer to heart action (p. 207) and in the second case: no indication of a cardiac difficulty was present (p. 203)

perceptible swelling contribute the essential features in the pathology of the thyroid gland in Basedow's disease. Those changes, to be sure, as a rule correspond to a distinct enlargement of the gland; but they are not necessarily dependent upon it. On the other hand, a rather large goiter can display only in circumscribed regions those alterations which must be called peculiar to Basedow's disease In any case, detailed structure and function of the gland can be altered for quite a while before its diseased condition becomes evident by its noticeable enlargement. That the familiar vascular thyroid gland signs can be evident without palpable swelling of the organ has already been mentioned (§13 and §24). Cases have occurred in which the evidence of an enlargement of the thyroid could not be found during life, afterward an unmistakable, symmetrical swelling was evident (see §20, above). As reported by Marie and Marinesco (1130), Joffroy and Achard (1119), both cases were combined with signs of tabes; Roper (1911) a 48 year old female; and Thorbecke (2589) a 28 year old patient.

Moutet (852) reported a 32 year old female patient who usually had no swelling of the thyroid At the time of menstruation, however, the size of the thyroid always increased distinctly Bradshaw (951) mentioned a 23 year old female whose thyroid swelling occurred only at times and was associated with pulsations in the neck (see also §30 above).

The goiter may appear many years later than the other Basedow's disease signs

I call to mind here the case mentioned (§237 above) by Williamson (1523) Gram (1316) reports a 27 year old patient who, for ten years, had signs of anemia, tachycardia, palpitation, occasional diarrhea, and tremor before the thyroid enlargement appeared In Krieger's (2305) case of a 46 year old female patient, a considerable goiter came only after palpitation, emaciation, weakness, sweating and diarrhea had improved and the exophthalmia which came last, had become reduced The pulse rate at that time was only 70 to 80 beats a minute during rest in bed

The number of cases mentioned in pertinent literature noting absence of goiter is not small. But the great difference in the statistical counts given (they vary from 0% to over 40%) makes it plain that the reason was either a quite different selection of patients or a varying degree of thoroughness and care in the making of the observations.

It must not be forgotten that the size of the goiter is subject to individual variation under normal circumstances The thyroid gland in the female sex is in general somewhat more voluminous than that in the male,[1] and in girls before puberty it is

[1] Aeschenbacher, Mitteilunger a d Grenzgeb d Med u Chir, XV Bd, 1906, p 288 J Holmgren (3137) has, by means of palpation, made the same observation but left it open as to whether this difference is not due to the greater difficulty of palpation in the male sex as a result of greater firmness of the soft parts

somewhat smaller than afterward (J. Holmgren 3137). J. Holmgren has, moreover, by means of a very efficient palpation method invented by him, shown that in women the thyroid gland in general lies somewhat higher up than in men and that in both sexes it gradually pushes downward in the course of time. In the lower position the lateral lobes are less easily reached by palpation.

If we omit the statistics of the surgeons, in which a goiter, for understandable reasons, is never absent, and among the other summations consider only those which include more than 30 cases, absence of a definitely palpable goiter amounts to 4%.

In the communications originating in the United States of America, from Clark (1546), Dock (2641), Thompson (2773) and Jackson and Mead (2968), concerning, altogether, more than 200 cases, goiter is never absent, the same is true of 38 cases assembled from St Bartholomew's hospital and several other London hospitals by S West In the case of one of his patients, a 26 year old female, the goiter disappeared during the period of observation and did not appear again, although the other signs continued Among J Russell Reynold's (932) 49 cases the goiter was absent once, among H Mackenzie's (2205) 52 cases, 5 times, and among G R Murray's (2553) 180 cases, 3 times The latter
cases a goiter was not evident
ble account given by the patie
also made a similar statement Among 58 cases of Dusch (207) the goiter was absent 3 times Among 47 cases from Mendel's polyclinic, assembled by Mannheim (1222) no thyroid gland swelling was discernible during the whole course as far as the case could be followed In 4 other cases it was absent at the time of the observation and *in the past history of the case a goiter was mentioned Pässler (1362) noted among* 51 polyclinic cases the absence of a goiter in 10, and Donchin (2644), among 46 cases from the Breslau medical clinic in 3 cases Chvostek (3219) was unable to remember any case in which alterations of the thyroid gland had not been present Among my own 103 cases, largely from the polyclinic, no thyroid-gland enlargement could be discovered in 8 patients, 4 men and 4 women In the case of a 27 year old female tachy-

(658) goiter was said to be absent in 14 cases or 43 75% W H Thompson (2443) stated that among 70 Basedow's disease patients 28 (40%) had no goiter Among A Vigouroux' (1014) 14 cases it was absent in 3 (21.43%) Besides the cases included in this collection I have been able to find in the pertinent literature accessible to me 106 more single observations in which the absence of goiter is reported In a few of these cases the disease had not been present very long and the observations covered only a short period, the others were incompletely developed forms of the disease.

In a number of carefully investigated cases, where the symptom complex was *otherwise well developed, no thyroid swelling was found during the entire period of* observation. Trousseau (128, 166, 219); Chvostek (269 13th observation); W R Thomas (572); R. Marcus Gunn (622); Cross (653) 1 case; L. Bruns (1024); M. Schmidt
tendency to atrophy")
nnelan (1295), Maybaum
el (2182), E. C Williams
(2441);

A 72 year old male observed by Topolanski (3199) had a rightsided high-degree exophthalmia and distinct lid signs on the right side only, tremor, high degree of emaciation, and temporary attacks of palpitation This patient previously had had a moderate goiter After the patient moved from the Steiermark to Prague, and later to Vienna, it disappeared entirely At the time of the observation scarcely a trace of the goiter could be discovered

In the cases of Heinlein (1584), Goris (1069), O'Carrol (2106), Sokolowski (2438) and Minkowski (2547a) only a little of the thyroid gland could be felt on the neck, but a more or less extensive goiter lay retrosternal (see §21 above)

§240. Tremor can be regarded as one of the most constant signs of Basedow's disease It is hardly ever absent during the entire course of the disease, as we have emphasized above (§108) and have verified by the statistical data. This sign is almost always present in otherwise incompletely developed forms, indeed it is sometimes especially well defined In Basedow's disease of children the tremor is found less frequently (see §281 below).

§241. Exophthalmia is the cardinal sign which is most frequently absent Also, in otherwise typically developed symptom complexes any indication of protrusion of the eyes may be lacking during the entire course, even when one or the other of the lid signs is present Sources of error in determining whether or not a slight protrusion of the eyes is present or not have been sufficiently indicated above (§35 and §43)

If we attempt to calculate the frequency of absence of this cardinal sign statistically, using only series of observations which include at least 30 cases, we find that among 1,415 cases exophthalmia was missing in 300, that is in 23 2%

In the various series the figures vary remarkably according to the case-history material coming under observation Among 58 cases observed by Dusch (207) exophthalmia was missing only 4 times, (6 9%), among cases from Garre's surgical material, Moses(2864) noted its absence twice (6 25%) and among Kocher's (2197) 80 cases it was absent 11 times (13 75%) Among Passler's (1362) 51 polyclinic cases it was absent 23 times (45%), and among 39 of the cases collected by Wilbrand and Saenger (2033) 12 times (30 77%) From my own series, the figure of 20% is about the average

In the American observations the percentage values vary between 2 13 (Clarke, 1546) and 36 25 (Thompson 2773), and the English between 2 63 (S West 686) and 27 65 (G R Murray 2553) Potain (493) estimates the absence of exophthalmia at about 50% In two large series of observations coming from Russia exophthalmia was missing in more than half of the cases Among 34 Basedow's disease patients from v Holst's (2385) observation only 2 had a high degree of exophthalmia "In the great majority there was an absence of any noticeable protrusion of the eyeball" Among Kroug's (2700) 106 cases exophthalmia was found only 45 times Among the earliest observers of Basedow's disease Caleb H Parry (8) and R J Graves (12) never seem to have been confronted by conspicuous protrusion of the eyes, while von Basedow (15, 23, 28) never failed to find it

Aside from the cases taken from the larger collections I found exophthalmia absent also in 227 single observations of otherwise well-developed cases. The number could be greatly increased if we wanted to include here the many more typical incomplete cases (see §242 below).

§242. A more exhaustive discussion is called for concerning those cases, by no means rare, which—whether of a long standing or recent—are associated with cardio-vascular symptoms, tremor, sweating and isolated neurological signs. Less frequently a rather wide gape of the lid aperture is also noticed The eye shows an increased stare (see §65 above) or the patients have a tendency to open the eyes wider when speaking emphatically.

Fr. Kraus (1871 and 2697) believes that these cases should be taken as a special disease group and under the title of "goiter heart" they should be separated from Basedow's disease and its incomplete forms

Among the cardiacs to be observed among those suffering from goiter there are doubtless cases which are to be traced to a completely or predominantly mechanical cause Above all, the difficulty or obstruction of breathing with either a superficial or deep goiter, especially in endothoracic goiter, may cause a sense of suffocation or contribute to the disturbances in the pulmonary circulation by obstructive effects of emphysema or bronchiectasia, and later result in myxedematous alterations of the right ventricle of the heart (dyspnoeic goiter heart) The thyroid-gland nerves as well *as the veins of the whole throat and face are greatly enlarged Sometimes* such patients also display isolated signs which do not find an explanation in a mechanical factor and resulting heart disease Examples are the fine tremor of the hands and nervous excitement

In the absence of any marked obstruction to breathing a mechanical factor can also produce cardiovascular complications from a simple goiter in another way. If the goiter is deep or retrosternal in position, the venous drainage toward the right atrium becomes more or less obstructed Together with the other factors this leads to congestion in the neck and thyroid veins and progression from a simple goiter to a so-called congestive goiter, or *struma vasculosa venosa* (Kocher) In such patients one observes not infrequently, together with the congestion, direct cardiac and circulatory disturbances, tachycardia, tremor, excitability, and sometimes protrusion of the eyes

The overactivity and dilatation of the heart, the tachycardia, and the congestion in the retrobulbar fatty tissue with slight exophthalmia are probably explained by this increased venous resistance. Kocher (2197) sees the evidence for this dependence of the above-mentioned manifestations of the goiter in the immediate disappearance of all the signs after removal of the goiter which is causing *the congestion. Furthermore,* re-

cent experiments on the effects of venous congestion in the thyroid gland by A Luthi (2707a) and T. V Verebely (2890) show more basic histologic changes in the thyroid gland, besides enlargement of the veins, impaired venous drainage and a swelling of the entire organ These include disappearance of the colloid, epithelial desquamation, and finally hyperplasia of the connective tissue. The consequences are an acceleration of heart action and an increase in nitrogen and phophorus in the urine. On these last points evidence has also been obtained by Blum by ligation of the blood vessels draining the thyroid gland. As a further mechanical cause for the vascular signs of goiter this has been postulated, especially in earlier work, as from pressure on the neighboring nerves in the neck Although, in quite isolated pathological-anatomical studies the occasional occurrence of such a relationship of the nerves in question appears possible, it must be recognized that only in exceptional cases is it a likely cause of the cardiovascular syndrome.

F V Birch-Hirschfeld, in his textbook on pathological anatomy (Vol 11, p 470, 4th edition, 1894) has reported an observation which belongs here The autopsy of a woman who had suffered for years from a peculiar heart disease characterized by tachycardia, irregularity, and dilation, as well as anxiety showed a firm nodular hypertrophy of the right lobe of the thyroid gland in the right thorax Several *nervi cardiaci* and especially the *ramus cardiacus* from the *ansa hypoglossi* were under pressure from this goiter

It cannot be forgotten that an interruption of the vagus influence on the heart produces an acceleration of the rate but no increase in the force of the heart action and would probably produce no noticeable enlargement of the heart It is known (see also §68, §164, and §168 above), that undoubted evidence of damage to the cervical *sympathicus* has been observed in single cases of goiter and Basedow's disease

In the majority of cases of Basedow's disease the complex of symptoms sketched above is independent of mechanical influences It is due exclusively to some influence on the regulatory mechanism of the heart and vessels It is possible to distinguish clearly this functional group of signs and symptoms from those which Riedel (1494) has already made the effort to separate from mechanically produced goiter disorders. The term thyrotoxic goiter heart proposed by Kraus (2697) and Kocher (2693) is certainly acceptable

Well-developed cases of this sort usually show a small soft goiter which tends to be congested with blood. Some, especially the older goiters, also contain nodules of cysts Such goiter is always freely moveable in the neck, has no retrosternal extension and causes no pressure manifestations.

The pulse rate as a rule remains between 90 and 120 But during complete rest and in the absence of any emotional excitement, or under anaesthesia, it goes down to 80 or lower During muscular activity the rate of the heart

beat usually rises considerably. The definitely dichrotic pulse graph leads to the assumption of a low tonus of the peripheral vessels, although, at the same time, the sphygmomanometer shows somewhat increased blood pressure Frequently, the patients suffer from periodic palpitation, sometimes this is combined with cardiac dyspnoea, and the force of the heart beat is considerably increased. Usually, distinct carotid pulsation is seen; sometimes other large arteries such as the aorta also pulsate. Such patients perspire easily Dermographism can often be produced. The tremor exhibits the character of typical Basedow's disease tremors, but it is usually noticeable only on the finger and sometimes the tongue. The occasional occurrence of a wide gape of the eyelids has already been mentioned above. The patients are easily excited They sometimes complain of headache and dizziness Exophthalmia, conspicuous emaciation and trophic disturbances are not observed in this type, but loss of hair may occur. Probably there is also an increase in the respiratory gas exchange. An occasional increase in nitrogen and phosphate turnover has been demonstrated. According to Burghart (2626a) alimentary glycosuria in case of goiter heart, as distinguished from typical Basedow's disease, is found only exceptionally. But one of these cases in which Fr. Kraus (984) found an unusual reduction in the tolerance for fructose, a 13 year old female patient, was cited by that author (1871) as a fine example of thyrotoxic goiter heart.

With longer duration and repeated exacerbations the above-mentioned sign becomes more marked. There is usually a widening of the cardiac dullness with lateral displacement of the cardiac apex beat This cardiac dilatation as a rule becomes reduced in rather a short time with a cure of the disease, either entirely or in large part.

The cases of thyrotoxic goiter heart occur predominantly in young people Young girls have a soft, diffuse swelling of the thyroid gland (a so-called *Blahhals* or puffed-up neck) They are pale and display the above-mentioned signs and easily give the impression that they are chlorotic. The blood, however, shows a normal or even increased number of red corpuscles and normal hemoglobin content Fr. Muller (2718) called this form pseudochlorosis. There are cases in which signs of thyrotoxic goiter heart accompanied by a marked growth of the goiter, appear at the time of the climacteric also.

Medications directed to act upon the goiter, such as iodine and thyroid-gland preparations also affect the signs dependent upon it very favorably, while they are harmful as a rule in typical Basedow's disease (see below under Therapy). An operative resection of the goiter in thyrotoxic goiter heart brings a certain and striking result. On the other hand digitalis, which is such a valuable medicine in other cardiacs, fails here as a rule.

The cardiovascular and nervous signs which group themselves around

the goiter and which form, mainly, the pattern of thyrotoxic goiter heart, can continue unaltered, with occasional fluctuations, for years without any further development in the direction of a typical Basedow's disease. With a spontaneous reduction of the goiter or a reduction achieved by therapy it usually disappears gradually and completely Long continuation may lead to no mechanical damage but to degenerative processes in the heart muscle, signs of premature senescence, poor nourishment, mental deterioration etc

In the goiter regions one not infrequently finds the symptom complex of thyrotoxic goiter heart while that of typical Basedow's disease is by no means common (see §298 below)

All the above-mentioned circumstances indicate that, in contrast to the symptom-poor forms of Basedow's disease, a certain nosological independence can be attributed to the thyrotoxic goiter heart.

We must, to be sure, differentiate rather carefully between this group and the mechanical cardiopathies, from dyspnoeic goiter heart, and from the congestive goiter mentioned above. But we must also point out here certain effects to be attributed to a pathologically altered thyroid gland. Although they are rather in the background as compared with the other more significant signs, yet there is a bridge here which leads to the cases of thyrotoxic goiter heart.

From the pathological viewpoint one must not lose sight of the fact that the thyrotoxic goiter heart is only one step in the series of diseases to be attributed to toxic influences on a thyroid gland which has been changed pathologically in a definite way This series begins with the artificial hyperthyroidism caused by feeding of thyroid and concludes with the many sided, symptom-rich *struma Basidowii* of Kocher

If we also grant the thyrotoxic goiter heart a certain independent identity, it cannot be denied that the dividing line between this and the symptom-poor forms of Basedow's disease is by no means sharply defined

In the majority of cases of goiter heart palpitations occur only occasionally, and the tremor is slight Yet cases do occur in which the cardiac palpitations are troublesome, and the patients seek medical aid because of this difficulty There are also others in which the tremor is so disturbing that the patients themselves are aware of it Marked tremor and pronounced nervousness are found especially when the symptoms of goiter heart appear in an individual with a nervous predisposition That the eye signs so characteristic of Basedow's disease are not entirely absent we have already mentioned above This is also admitted by Kraus He prefers to attribute unilateral exophthalmia to mechanical damage to one or both cervical *sympathici* This, in my opinion, can hardly be applicable, or at most only in special cases I have not been able to convince myself that an abnormal width of the pupils, as Kraus relates, belongs to the signs of goiter heart

Although gradual transition from the symptom complex of goiter heart to typical Basedow's disease is not seen as a rule, yet cases are known of patients who have suffered for some time from tachycardia, palpitations, tremor, and nervous excitability, as well as from goiter. There sometimes appears in rapid succession a further series of signs, or a Basedow's disease in more severe form may develop following severe emotional shock, infectious disease, pregnancy, gynecological operation, use of thyroid tablets, or even without any apparent cause Rudel (1494, p. 476), Kroeger (2397), Sokolowski (2438), M. V. Ball (2453), H. Brooks Wells (2597), Andebert (2606), Lewellys F Barker (2803), Gitterman (2829a) and others have observed such cases (see also §248 below).

Evidence of the close connection between thyrotoxic goiter heart and typical Basedow's disease is furnished by the fact that, if several illnesses occur in one family, not infrequently one member of the family displays the clear pattern of Basedow's disease and another the signs of thyrotoxic goiter heart (see §285 below)

§243. In a relatively large number of cases the typical symptom complex of Basedow's disease appears as a complication of a simple goiter which has been present for a fairly long time This change is usually preceded by a renewed growth of the goiter and may become complete rather rapidly. Occasionally the process becomes acute (see §253 below): cases of Kocher, Ganthier, Zuber and others. This goiter then assumes, as a whole or in part of its structure, the anatomical and clinical characteristics of a typical Basedow's disease goiter The immediate cause is sometimes emotional shock, infectious disease or pregnancy. This may occur after the thyroid gland had gradually become enlarged, perhaps already during an early pregnancy, the beginning of the climacteric etc. Occasionally the appearance of the Basedow's disease syndrome has been observed following surgery upon an ordinary goiter (see §217 above in one case of Nelaton, and §253 below, in the case of Roser, Trevenot, Kocher, Kraus, Brieger). In other cases, the use of thyroid preparations for the purpose of reducing a simple goiter has brought about the appearance of Basedow's disease signs, more rarely of a complete Basedow's disease (see §248 below, cases of M. V. Ball, J. Rogers, and §253, cases of Kocher, Elliot). Sometimes these changes occur without apparent cause, as for example in a case of Gauthier (1104), a 50 year old man, and in the case of Kocher's 8 year old boy (see §253 below) The symptom complex in this group of cases is often incomplete, *exophthalmia often being absent.* Nevertheless, the expert will hardly be in doubt that he is dealing with real Basedow's disease.

If one wishes to designate by a special name the cases in which the Basedow's disease signs appear as a complication of a simple goiter of some dura-

tion, the name of *struma Basedowificata*, as suggested by Kocher (2693 and 2693a) seems to me to be the best. In France the name of *goître basedowifie* was used by Pierre Marie (1618). Also, there is no objection to the term "secondary Basedow's disease" (Mobius, 1478 and 2717, p. 62), *goître exophthalmique secondaire* (Gauthier 896 and 1198), if one just keeps in mind that this refers to a real, but often less symptom-rich Basedow's disease which is not distinguishable from genuine Basedow's disease by any essential feature. The course of the cases of secondary Basedow's disease is, to be sure, frequently mild They furnish an especially rewarding object for surgical interference

Bruhl (956) and Duhamel (1192) are entirly mistaken when they speak of a false exophthalmic goiter in order to distinguish cases of Basedow's disease with goiter from genuine Basedow's disease which they regard as a neurosis

Buschan (1181) uses the term "secondary Basedow's disease" in the same sense as symptomatic or pseudo-Basedow's disease He believes that this form of the disease is due to certain states of irritability, especially paralysis in the *vagus* and *sympathicus* arising as pressure affects the goiter Hereby he accepts a reflex action as the basis for those cases in which cardiovascular signs go with the goiter These are complicated by severe nervous or mental manifestations, and so "may be mistaken for a genuine Basedow's disease" The reflex action in easily excitable persons with a nervous predisposition is transferred from the affected thyroid gland, by way of the *nervi laryngii*, to the vasomotor centers For an evaluation of this interpretation I refer to what has been said above concerning the mechanically caused goiter cardiopathia

Kocher (2197) used the expression "pseudo-Basedow" for the conditions which we have characterized above as congestive goiter, *struma vasculosa venosa*

Having become acquainted with the various forms in which thyrotoxic symptom complex may appear as a complication of goiter, it will not be without interest to consider more closely the relative frequency of these various forms, as shown by larger series of observations

Kroeger in Riga (2397) studied 130 persons with thyroid enlargement ranging from the slightest, barely palpable rounding outward to pronounced goiter of soft consistency Among 24 only an increase in the force of heart action was objectively distinguishable, among 36, besides the increased force of the heart action and a distinct carotid pulsation, there was also tremor, nervous excitability, restlessness, heat sensations, and disturbed sleep Thirty-one cases showed the characteristic signs of a completely developed Basedow's disease

Gitterman (2829), physician at Bad Nauheim, saw, among 121 patients, 21 men and 100 women who had a distinct, but, in most cases, small goiter and a myogenous heart disorder, 11 of these cases had definite Basedow's disease In 110 patients the goiter had been present for only a few years, and during that time a disorder of the heart muscle had developed which Gitterman attributed mainly to a thyrotoxic action In 31 of these cases it was a simple cardiac dilatation Among these, 13 had a continuous rapid pulse and 18 had periodic attacks of tachycardia. Usually there were also sensations of palpitation Twenty-three had tremor and general nervous

symptoms, 8 showed an indication of exophthalmia (perhaps only a wide gape of the lid aperture) The entire symptom complex of Basedow's disease appeared only in 1 of these cases and this occurred under the influence of violent nervous excitement The congestive symptoms which must be considered indications of local *pressure* appeared only 8 times among 110 patients.

Among 80, mostly typical cases of Basedow's disease, including in part incompletely developed cases which A Kocher (2194) has collected from his father's wealth of observation material, 25 had had more or less of a goiter since childhood or puberty In 3 cases, according to the statements of the patients, the goiter did not develop until later in life. Its development preceded the Basedow's disease signs by 3, 8, and 12 years respectively In 20 of these cases goiter was present in the family Seven came from well-known goiter regions In 18 cases, rapid growth of these goiters occurred without known cause at the same time that the first signs of Basedow's disease began to appear

In 1906, Th Kocher (2693a) *reported that he had treated 14 cases with the signs* of goiter heart, 4 by internal medical measures and 10 operatively by ligature of the thyroid arteries or unilateral excision of the goiter, all of them successfully. He has seen 72 cases of *struma basedowificata* and operated upon 60 without any casualties Of the 53 patients about whose later condition he could obtain information 51 were cured and 2 improved A hundred and forty of his patients had typical Basedow's disease, 106 of these were operated on

Kreeke (3146) estimated that about 70% of his cases of thyroid disease had goiter-

in the form of a salve to reduce a goiter which she had had for two years

Among 24 patients from the surgical clinic in Zurich, as summarized by B Wittmer (2034), a thick neck or a pronounced goiter which had been present for some time before the occurrence of the Basedow's disease signs, was found in 19 cases

Among 18 of the cases collected by Hunerfath (1735) from the Munich medical clinic 2 had had a goiter since childhood and 2 had had one for three to five years In one of these cases the goiter began to grow larger following the development of the other Basedow's disease signs and after the third delivery Among Hirschl's 20 cases of Basedow's disease (2192) 3 patients, aged 30, 40 and 70 years respectively had had goiter since childhood In the case of one of these patients the size of the goiter began to increase after marriage After a ten-year interval a new growth phase began Soon the signs of Basedow's disease developed In another case the goiter began to increase after the first delivery and the accompanying excitement (the child was illegitimate) At the same time all the other signs of Basedow's disease appeared In the third case a visible increase in the size of the goiter occurred after the first appearance of the menses and again later *after the fourth pregnancy Violent mental* excitement set off the rather acute course of the Basedow's disease

Among 45 Basedow cases assembled from the Breslau clinic by Boris Donchin (2644) 9 had had a goiter many years before the outbreak of the disease. In the case of a 30 year old woman, the goiter had developed seven years before, in connection with a birth; six years later all the other signs appeared. In the case of a 27 year old female the goiter preceded the acute illness by ten years, in the cases of 3 older women and that of a 51 year old man the goiter came first by several decades. In the case

of an 18 year old woman, a 34 year old female, and of a 41 year old patient, the goiter had been present since childhood

As K Schultze (2750) reports, 19 out of 50 Basedow patients under observation by *Riedel had already had goiter for a long time, and a few for decades* In most of these cases the signs of Basedow's disease were ushered in by a sudden growth of the goiter In the case of a 44 year old female who had been burdened with a goiter since her seventeenth year, the goiter had recently become smaller. For three months there were palpitations. Soon the other signs of Basedow's disease appeared. During an operation a large substernal and subclavian goiter was found

H Moses (2864) described among Garre's 32 cases, 2 with so-called secondary Basedow's disease In the case of a 54 year old woman a rightsided goiter had been removed eight years before, five years after this operation she noticed a swelling *on the left side of the neck Two years after that a walnut-sized goiter nodule was* enucleated A year later the woman noticed a renewed thickening of her neck and in

changed, then it began to grow and for four months she slept poorly, had a feeling of depression, excitability, palpitation, tremor, and, later, exophthalmus

H Mackenzie (918) stated that he had seen at least 2 among more than 30 cases in which the goiter was present before the other signs appeared In one case an uncomplicated parenchymatous goiter had been present for six years This was ultimately complicated by permanently rapid pulse, tremor, emaciation, and increased irritability Maude (1133) studied carefully 7 cases in which Basedow's disease attacked persons who had already had goiter for a long time

Among Murray's (2213) 120 Basedow *cases there were, he states, at least* 14 in which a goiter preceded the development of the other signs by a number of years, once by 34 years, another time by 32 years in other cases by 25, 18, 12, 10, 8, 6 and 3 years respectively In 1899 he saw 2 siblings, a 19 year old man and a 16 year old girl, each of whom had a soft parenchymatous goiter of moderate size He saw them both again two years later, each with clear-cut Basedow's disease although the goiter had not noticeably increased in size

Among 9 of Huntington's (2519) patients who had been operated for Basedow's disease, 5 had had a goiter for 35, 34, 13, 10 and 6 years respectively

Dock (264) counted 12 among 32 cases of Basedow's disease in which goiter had been present 3 to 37 years before the other signs were noticed

Among 17 of the Basedow's disease cases of Shepherd, who were operated, (2755) 10 had had a small or large goiter preceding the outbreak of the other signs of this illness by several years A few had enlarged necks from childhood In the case of a 34 year old woman a more rapid growth of the goiter began during her two last pregnancies, in the case of a 30 year old woman this occurred following the last delivery Among 61 cases observed by Frank Billings (2806) a goiter had been present in the case of 20 women and 1 man for from 3 to 20 years before the signs of Basedow's *disease appeared*

Our own Basedow's disease material originated largely from goiter free areas. There were only 8 among 108 cases, with the exception of 3 perfect "goiter heart" cases, in which a simple goiter had been present for many years, or since childhood Later, sometimes with a rapid growth of the goiter, the Basedow's disease signs developed more or less suddenly In the case of a 33 year old woman the neck became more enlarged following pregnancy, and finally palpitation, tachycardia, and tremor

arose There are numerous isolated observations of the appearance of Basedow's disease complicating an ordinary goiter of long standing.

Especially pertinent cases of this sort are described by Ronzier (92), MacNaughton Jones (316), Benard (512), and Gaill (544) Story (571) reports a case in which the sisters of the patient had simple, uncomplicated goiter. Ehrlich (888) reports an 11 year old girl whose goiter was said to have appeared shortly after birth. Bruhl (936) reported a case Lamy (986) reports that the goiter had appeared 25 years before See also Lasvenes (988, 3 cases), Boeckel (1021) Maude (1036), (the goiter had been present for 24 years), Gauthier (1104), (in one of his cases the course was turbulent, see §253 below) Joffroy (1117), Tillaux (1167), Walther (1676), Morestin (1889) 2 cases, Richelot (1906), Fr. Muller (1134, 2 cases; in one of these the grandmother, mother, and 3 sisters of the patient all had uncomplicated goiter), Hohl (2680 2 cases), W Gilman Thompson (2773), H Moses (2864) and Viannay (3073 and 3074)

§244. Basedow's disease signs have been observed in cases of carcinomatous and sarcomatous degeneration of the thyroid gland.

In 1875 Cornil[1] described a case of epithelioma of the thyroid gland, a 76 year old man Here, except for the tumor located in the left thyroid gland lobe, only a rapid pulse up to 90 beats per minute was noted Three days before death occurred from pneumonia a slight exophthalmia on the left side and a distinct enlargement of the left pupil appeared, both manifestations which can probably be attributed to stimulation of the *sympathicus* The swelling had increased more rapidly in the last two months following a fall from a wagon In this accident the man had almost strangled himself Finally, he had great difficulty in swallowing The swelling was the size of a turkey egg In one place, it was attached to the esophagus Several small tumors protruded under the mucus membrane of the esophagus The part of the thyroid gland occupied by the tumor appeared white in cross-section A milky fluid scraped from it contained large rounded and irregularly-shaped cells. The histological appearance corresponded neither to the usual pattern of an epithelioma, nor to that of a glandular carcinoma. The author assigns to the tumor a position *intermédiaire entre les diverses formes de l'épithéliome* Several of the accompanying illustrations show a pattern which is also found in the typical Basedow's disease goiter (see Pathological Anatomie below)

Bénard (512) in 1833, reports in his thesis, a case of Tillaux under the heading *Sarcome du corps thyroïde ayant donné lieu à tous les symptômes du goître exophthalmique* A 33 year old man had noticed a swelling of his neck a year before Two months later the eyes gradually began to protrude and the palpitation, which had been slight at first, became very troublesome Also, his breathing became difficult All the symptoms increased in intensity and attacks of strangulation occurred during which profuse perspiration broke out on the upper part of the body Since the situation became more and more threatening and hoarseness of the voice developed the patient decided upon a thyroidectomy which Tillaux performed In spite of a complicating erysipelas the cure was complete. All the Basedow's disease signs disappeared The histological examination showed fibrosarcoma of the thyroid gland Since a more exact description is lacking, the correctness of the diagnosis cannot be determined

Before the Greifswald Medical Society Mosler (924), in 1890, demonstrated a man with no hereditary history A tumor had arisen on the right side of the neck

[1] Sur le développement de l'épithéliome du corps thyroïde; archives de Physiologie normale et pathologique, XII, p 659

rather rapidly. In 5 days, it had attained the size of a child's fist The tumor, which caused difficulty of breathing and swallowing, was well circumscribed, notably hard, and displayed an irregular surface In direct connection with this, and located somewhat medially in relation to it, another nodule of the size of a hazel nut was evident *Bruit* and pulsation were absent. On the right side, v Graefe's sign was discernible. Heart action was regular and pulse full at 68 per minute Neither nervous or other Basedow's disease signs were evident The diagnosis was scirrhus tumor of the thyroid, and the patient was referred to the surgical clinic A promised further report of this case has not, to my knowledge, appeared

In a case reported in 1892 by E Boeckel (1021), that of a 48 year old woman who had a swelling on the neck for 10 years, pronounced Basedow's disease signs arose, at times together with occasional enlargement of the tumor These manifestations consisted of strong carotid pulsation, moderate protrusion of the eyes, loss of appetite, and emaciation They lasted five or six days, and then disappeared gradually. But each time the tumor of the left thyroid lobe remained increased in volume Microscopic examination, made by v Recklingshausen show a large cell sarcoma *surrounded by nearly normal thyroid-gland tissue Three years later a recurring* lump the size of a hen's egg was removed, this consisted entirely of sarcoma tissue with numerous giant cells

Mikulicz (1350) mentioned in his lecture on the surgical treatment of Basedow's disease, but without giving further details, that in 1 case he had found a lymphangioma instead of a Basedow's disease goiter

Rehn (2009) reported, also without further details, that in a case of Basedow's disease Helfrich had intended to perform a goiter operation, death occurred during anaesthesia and a carcinoma of the thyroid gland was found

Among the 9 cases of Basedow's disease reported by Hamig (1508) he renders an exact account of the histological evidence regarding the thyroid gland These included one in which the tumor proved to be a medullary carcinoma (p 9 and 26 of the thesis)

A 34 year old woman had had a walnut-sized goiter for 12 years, this began to grow larger for a year Seven or eight months later palpitation, tremor of the extremities and hoarseness developed The patient felt weak and her personality seemed changed Pulse varied between 120 and 156 beats per minute There was strong carotid pulsation, but no exophthalmia The goiter was fist-sized, nodular, and hard The specimen obtained after a left thyroidectomy comprised a rounded mass with uneven, knotty surface In cross-section it showed a lobed structure The whitish fluid obtained by scraping the cut surface contained a large number of polygonal epithelial cells with relatively large nuclei The whitish regions which produced much fluid showed in the section a network with wide trabeculae composed of epithelial cells of similar appearance In between, a delicate stroma chiefly formed by vessels was found The cells of the swelling filled the spaces of the meshwork almost completely They were noticeably rich in glycogen, while the typical Basedow's disease goiter, also according to observations of my own, is glycogen poor. There were no more colloid globules within the cell masses in the peripheral parts The regions immediately beyond the thyroid gland showed the structure of a parenchymatous goiter with relatively scant colloid In one place a breakthrough of the swelling into the lumen of a vein was observed Following the operation, all Basedow's disease signs disappeared No relapse had occurred after three and three quarter years

Harmer[1] described a peculiar case which belongs here A 44 year old woman noticed

[1] Schilddrusenmetastase in der Nasenhöhle Wiener Klin Wochenschr XII no. 23, p 628. 1899.

that after the last delivery, two and one half years before, a lump on the right side of the throat, larger than a nut, had developed. It grew at first slowly and then rapidly Headaches in the forehead region occurred, together with a ptosis, first of the left upper eyelid, and later of the right one. There was diminution of vision in the left eye and then in the right The left side of the nose was obstructed. A delicate tremor of the hands was noted Rapid pulse up to 120 beats per minute, occasional palpitation, and exaggeration of the tendon reflexes became evident Furthermore,

cavity On the right a flat compressed swelling of soft consistency was located Microscopic examination of the nasal tumors showed a medullary carcinoma. From the peculiar glandular structure, and the presence of cavities filled with a colloid mass, a metastasis, arising from the thyroid gland, was recognized and the tumor in the latter also pronounced a carcinoma Subsequently, a few small hard lymph gland swellings appeared behind a very hard thyroid gland tumor which had become larger than a man's fist There also was a diminished resonance over the sternum The point of origin of the metastatic tumor was found to be at the base of the skull in the sphenoid bone No extirpation of the thyroid gland tumor was undertaken, and nothing further is reported about the outcome

sides of the throat The pressure signs increased, and the patient became cachetic Nothing is mentioned as to the form of the cachexia, or as to the metabolism investigation (see §223 above). Also, no anatomical examination was made. But the clinical finding and the age of the patient favor the assumption made by Carrell. According to Ehrhardt 26 67% of all the cases of carcinoma of the thyroid gland which he has known occurred between the ages of 50 and 60, and 58 67% between 40 and 60

Among the 26 case histories of *struma maligna* described by Ehrhardt[1] in his exhaustive treatise concerning the anatomical and clinical conditions of this type of goiter, there is one in which clear Basedow's disease signs are described (p 425). A 52 year old woman, previously healthy, noticed a year before admission a slight swelling on her throat which became slowly enlarged Then, nervous excitement and tremor of the hands occurred, the eyeballs protruded somewhat and the patient often suffered from palpitation and shortness of breath The pulse rate was 120 The proposed operation was declined A severe attack of dyspnoea made a tracheotomy necessary A few weeks later Freiherr v. Eiselberg performed a strumectomy of the right side However, this operation could not be carried out in the usual way In one place the tumor, a wart-like elevation, had broken through the capsule and, beneath the goiter, had become firmly attached to its surroundings Also, the left half of the thyroid gland appeared enlarged, showed scirrhous degeneration, and involved the trachea and esophagus to such an extent that these also were extirpated The isthmus and a part of the right lobe were left. Following the operation the Basedow's disease signs soon disappeared But the dyspneic difficulty remained. After about half a year the woman died from a severe local relapse with extensive metastasis. Microscopic examination showed a cancerous nodule in the right thyroid lobe, and a scirrhous carcinoma in the left

[1] Zur Anatomie und Klinik der Struma maligna Beitrage zur klinischen Chirurgie XXXV. p 343 1902

A peculiar case in which, the symptom complex of Basedow's disease appeared shortly before death, is described by R Hirschfeld (2674). The 36 year old female patient was under treatment because of an inoperable sarcoma of the left iliac bone She died with signs of pneumonia a week after her admission to the Freiburg psychiatric clinic. The autopsy showed in addition to the large tumor in the iliac bone, numerous metastases in the liver, pancreas, kidneys, mediastinal glands, ribs, and both lobes of the thyroid gland The larger of these thyroid tumors measured 6 by 3 by 1 cm, three others were the size of cherry stones, of rather firm consistency and of whitish color They did not show regressive changes as did the parent swelling and the other metastases The parts of the thyroid gland which had remained unaffected appeared as a colloid goiter of moderate degree The follicles contained rather abundant colloid and were somewhat flattened in the neighborhood of the tumor During her lifetime an enlargement of the thyroid gland had not been noted While in the case just described the tumors in thyroid gland were almost certainly of metastatic origin, it was presumed in a case reported by K v Stejskal (3058) that a malignant tumor had developed in the parenchymatous goiter which had been present for fifteen years and that the tumor had caused the numerous bone metastases In the case of a 55 year old woman, two soft pulsating swellings were found, one on the forehead and one on the back of the head where it had eroded the bone A similar tumor on the left thigh had caused a spontaneous fracture Recently clear signs of Basedow's disease had become evident tachycardia, exophthalmia, tremor of the extremities, frequent attacks of perspiration, diarrhoea, and irregularity of the pupils Clinically, however, no alteration of the goiter as compared to its earlier state was evident.

Th Kocher mentioned a case of columnar cell cancer (Langhans) in a 53 year old man in his valuable work on the clinical recognition of malignant tumors of the thyroid gland[1]

Three and a half years before, a leftsided goiter operation had been performed on this man because of breathing and swallowing difficulties caused by a walnut-sized non-painful tumor A year later, a renewed growth of the swelling was noticed Iodine sprays were applied without the slightest result Thyroid tablets and iodothyrin were given internally Emaciation, tachycardia, general weakness, tremor and nervousness followed. The recurring tumor under the scar was one and a half times the size of a fist It was of firm, elastic consistency, and not easily palpable The right thyroid lobe was small and hard The thick overgrowth made a routine operation impossible Death followed three days later No autopsy was performed

In a case reported by J Clunet (2927) Basedow's disease signs appeared in a pronounced form, although almost the entire thyroid gland was replaced by the cancerous new growth The autopsy showed distinct changes also in the other glands of internal secretion

Two cases which belong here have been published by J Lowy (3152) from the Landeskrankenanstalt in Brunn In the case of a 18 year old working girl, 16 months before, a goiter which had been present for years started to grow rapidly, without known cause, finally leading to difficulty in breathing After a goiter operation on the left, where a simple colloid goiter was found, the patient felt entirely well for several months Then, a swelling arose on the breastbone Almost at the same time pains at the back of the head appeared, palpitation, and weakness of the left upper extremity There now was a tachycardia of up to 170 beats per minute, exophthalmia, and infrequency of involuntary blinking, furthermore, several nodules larger than hazel nuts on the left side of the throat appeared, and a swelling of elastic texture

[1] Deutsche Zeitschrift für Chirurgie XCI p. 227, 1908

occupied the region of the *manubrium sterni*. Mobius's antithyroidin was administered A few months later the patient died. No autopsy was performed The author presumed that it had been a case of metastases from a thyroid gland tumor which had still been benign at the time of the operation

The second case was a woman of 31 who had a swelling in the region of the thyroid gland for seven years, and in the final years noticed a rapid growth of the swelling Five months before, palpitation and lumbar pains had arisen and three months previously the patient noticed a swelling on the right side of the head which increased rapidly in size Soon still another swelling arose on the skull. Almost simultaneously with these, paresthesia and weakness in the legs occurred Besides the changes described v Graefe's sign and v Stellwag's sign were found, in the region of the thyroid gland a lobulated firm tumor was noticed The tumor increased in size Five months after the onset death occurred The autopsy showed a medullary carcinoma of the thyroid gland with multiple metastases in the skull, the breast bone, the ribs, the body *of the fifth cervical vertebra, several thoracic vertebrae,* in the right thigh bone, lungs, liver, kidneys, and lymph glands The thyroid tumor showed a definite glandular structure in places Like most of the metastatic growths, which in their histologic structure conformed entirely with the primary tumor, it contained only a little colloid

Very recently, Kuchendorf[1]*, an Army Medical Corps Officer, reported that,* in the case of a sergeant who had suffered for several years from the signs of Basedow's disease, a fist-sized, knotty swelling had been removed from the right side of the neck Microscopic examination proved this to be malignant goiter "probably can-

the same time the Basedow's disease signs improved greatly The pulse was 68 and regular The eyes still protruded to some degree A convalescent sojourn at Bad Nauheim led to complete recovery such that the man was able to resume his military duties and even participate in maneuvers without difficulty

This survey of the known cases of malignant goiter with Basedow's disease shows that, in view of the infrequency of malignant goiters, such complications occur only exceptionally. Kocher, in 1908 (l.c p 198) estimated approximately 400 malignant goiters had come under his observation.

Among 16 cases of *struma maligna basedowificata* 11 were identified as carcinoma of the thyroid gland (columnar cell cancer, medullary cancer, cirrhosis) 3 as sarcoma; in 2 cases the nature of the new growth is not ascertained (in the case of v. Stejskal and the first of Lowy) Also, in the case described by Carrel as cancer of the thyroid gland no strict proof of the cancerous nature of the neoplasma is submitted Kocher (l c p. 197) calls attention, with reference to Professor Langhans, *to the unusual difficulty* frequently encountered in the histological diagnosis of malignant thyroid gland tumors. In their clinical behavior carcinoma and sarcoma of the thyroid gland have much in common. In all cases in which an extensive

[1] Deutsche Med Wochenschr; 1910, XXXVI, no. 21, p. 985.

case history is available, a swelling of the neck has already been present for a long time (1 to 15 years). Then a rapid growth of the swelling occurs. *In several cases metastases soon made themselves evident, some very early.* In a few cases these metastases were the reason why the patients called on the doctor (Harmer, v. Stejskal, in Lowy's two cases) With the beginning of the rapid growth, several times only upon appearance of the metastases (Harmer, v Stejskal, *both cases of Lowy's*), *the Basedow's disease signs* appeared Sometimes these were only slightly developed (in the cases of Cornil, Mosler, Harmer); in other cases, however, they appeared very distinctly, *and in full number* In Kocher's case the *thyroid gland therapy* which was begun at the time of the renewed growth of the swelling must also be considered a contributing factor (see also §253 below) In the case of Hirschfeld the primary tumor was located in the iliac cavity Only after the appearance of *sarcoma metastases in the thyroid gland did the Basedow's disease symptom complex appear* In 4 cases, the Basedow's disease manifestations disappeared promptly after excision of the thyroid gland swelling, in 1 case after exposure to X-rays In 1 case, death occurred during anesthesia and in 3 it occurred *after the operation* From a practical standpoint it is naturally of the greatest importance to establish the diagnosis of a malignant goiter as soon as possible For it is clear that, in such *cases medical-dietetic therapy would be merely lost time and only the operative removal of the affected parts of the thyroid gland can be considered* In regard to the often very difficult diagnosis of the malignancy of a goiter in the early stages of the malady I must refer to the works of Ehrhardt and Th *Kocher quoted above*

It is difficult to explain the occurrence of the manifestations of hyperthyroidism or the symptom complex of Basedow's disease in malignant goiters. It is possible that, because of the development and growth processes *of the new formation in the thyroid gland, similar alterations are produced* such as would result from other influences acting upon it (see §253 below, also Etiology and Pathogenesis)

In the case of Boeckel and v Recklinghausen the sarcoma was enclosed by "nearly normal" thyroid-gland tissue In Harmer's case the parts which remained unaffected by the cancerous degeneration showed the structure of a parenchymatous goiter with relatively scanty colloid, and in Hirschfeld's patient the thyroid gland *in the region surrounding the sarcoma nodules showed the pattern of a colloid goiter of moderate degree with flattening of the follicles in the proximity of the tumors*

On the other hand *it* has been shown that cancerous new growth in the thyroid gland and metastatic tumors arising from it sometimes show a structure which corresponds in many ways to the typical Basedow's disease goiter

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[1] Deutsche Med. Wochenschr, 1910, XXXVI, no. 21, p. 985

of perspiration or from dry coughing; in many cases watery diarrhea occurs.

Caro (2921) found that the blood count in incompletely developed cases differed from that of normal blood in the same way, as in typical Basedow's disease, except to a lesser degree (see §227 above). The investigations of J. Gordon and N. v. Jagic (2590) have shown that the blood count does not depart noticeably or at all from that of the classic form There is an almost constant lymphocytosis and a considerable increase of mononuclear leucocytes as compared with the polymorphonuclear neutrophils

In 6 typical Basedow's disease cases the count of the red blood corpuscles was 4,500,000 to 5,700,000/cmm, that of the white cells 3,000 to 12,000 The polymorphonuclear neutrophil cells formed 57 4% to 68 2% (compared to 72% normal), the

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and the mast
ch seemed to
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Kurlow (3147) at the Internal Medicine Clinic of the University of Tomsk, found the white cells were increased somewhat All the leucocytic forms were included in

The development of the disease in these cases almost always is slow and gradual Certain disturbances, such as nervousness and palpitation, often date from an earlier period of life The disease signs are fluctuating, improvement and exacerbation often alternate with one another The disease may continue for years, or decades, without the tendency to develop into a complete, severe form of Basedow's disease. Nevertheless, cases come under observation now and then, where, because of definite immediate cause, such as violent emotional shock, acute infectious disease, or beginning of the climacteric, a typical Basedow's disease develops gradually or rapidly

P Marie (555) in his now famous thesis was the first to describe and explain a large number of incompletely developed cases of the form with which we have been dealing in these paragraphs He explained that they are very frequent Also, Gordon Dill (1098) reports a number of such cases, and likewise W C Krause (1598), Harry Campbell (2158), V Holst (2385) and Sawyer (2878)

Recently R Stern (3060) made an attempt to assure a nosological independence for these cases He attempted to establish that they showed, in contrast to the classical form, a series of important differences in symp-

This occurred in Cornil's and Kocher's cases. Of the medullary carcinoma investigated by Hamig the more peripheral parts contained small colloid globules within the cellular matrix. The metastatic cancerous tumor in Harmer's case showed, in places, a glandular structure with colloid-filled spaces, and in Lowy's second case the pronounced glandular structure of some parts, with scanty colloid in the thyroid gland tumor as well as in the metastases, was emphasized.

It is not impossible that in exceptional cases cancerous thyroid tumors and their metastases can cause changes in organisms analogous to the otherwise benign, diffuse hyperplasia of these glands. Highly instructive in this regard is v. Eiselsberg's observation.[1]

After extirpation of a carcinoma which occupied the larger part of the thyroid gland the manifestations of *cachexia strumipriva* appeared These improved when a metastasis had formed in the breastbone. After its excision signs of cachexia recurred. When we see that a cancerous metastasis can take over the functional activity of the parent organ up to a certain degree, we can understand that it might be able, by an altered functional activity in a certain direction, to bring about Basedow's disease signs. We have seen that, in the cases of Harmer, v. Stejskal and Lowy, the Basedow's disease signs appeared only after the appearance of the metastases. It is also noteworthy that in so extensive a cancerous degeneration of the thyroid gland as that of Glunet's case, pronounced Basedow's disease signs arose and not manifestations of *cachexia strumipriva*. Other glands of internal secretion seem to have participated here vicariously to a certain degree

§245. Among the disease forms associated under the title of thyrotoxic goiter heart, goiter and cardiovascular signs predominate. In another very extensive group of incompletely developed cases the nervous signs stand out more prominently The thyroid enlargement is sometimes only slight, or only discernible upon special examination Besides continuing or recurrent tachycardia and palpitation, there is characteristic tremor, general nervousness, psychic and motor restlessness, rapid fatigue, sleeplessness, and loss of strength, all of which form the combined symptom complex of the case history. Such patients are often treated for neurasthenia without noticeable success or are sent to spas on account of anemia. It can not be denied that such cases sometimes remain obscure for a while and that they can cause considerable diagnostic difficulty It is here, therefore, that the presence or occasional occurrence of certain conspicuous secondary signs, the results of blood tests, and the testing of the respiratory quotient is of decisive significance.

Sometimes one or another of the eye signs such as a wide opening of the lid aperture is discernible; more rarely also a slight degree of protrusion of the eyes. The patients often suffer from localized or general outbreaks

[1] Archiv fur klinische Chirurgie XLVIII, p. 488.

of perspiration or from dry coughing, in many cases watery diarrhea occurs.

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In 6 typical Basedow's disease cases the count of the red blood corpuscles was 4,500,000 to 5,700,000/cmm., that of the white cells 3,000 to 12,000. The polymorphonuclear neutrophil cells formed 57.4% to 68.2% (compared to 72% normal), the lymphocytes 24.8% to 34.8% (compared to 24% normal), the mononuclear leucocytes 4% to 9% (compared to 2% normal), the eosinophils 2.6% average (compared to 2% normal) and the mast cells 0.3 to 1%.

In 6 incomplete cases of the form of the disease in question the blood count showed red cells 3,700,000 to 6,200,000 per cmm., white cells 4,560 to 8,260. The polymorphonuclear neutrophils made up 53.5% to 67.3%, the lymphocytes 21.2% to 39%, the mononuclear leucocytes 2.7% to 13.5%, the eosinophils 4.2% average, and the mast cells 0.2% to 1.3%. Sawyer (2878) also noted in his cases, many of which seemed to *belong to this category of incompletely developed forms, the frequent occurrence* of large mononuclear leucocytes in the blood.

Kurlow (3147) at the Internal Medicine Clinic of the University of Tomsk, found the white cells were increased somewhat. All the leucocytic forms were included in this increase, but particularly the large mononuclear cells. Fully developed cases, on the contrary, show a decrease of the white cells. This occurs chiefly at the cost of the neutrophil polymorphonuclear cells.

The development of the disease in these cases almost always is slow and gradual. Certain disturbances, such as nervousness and palpitation, often date *from an earlier period of life. The disease signs are fluctuating, improve*ment and exacerbation often alternate with one another. The disease may continue for years, or decades, without the tendency to develop into a complete, *severe form* of Basedow's disease. *Nevertheless, cases come under* observation now and then, where, because of definite immediate cause, such as violent emotional shock, acute infectious disease, or beginning of the climacteric, a typical Basedow's disease develops gradually or rapidly.

P. Marie (555) in his now famous thesis was the first to describe and explain a large number of incompletely developed cases of the form with which we have been dealing in these paragraphs. He explained that they are very frequent. Also, Gordon Dill (1008) reports a number of such cases, and likewise W. C. Krause (1508), Harry Campbell (2158), V. Holst (2385) and Sawyer (2878).

Recently R. Stern (3060) made an attempt to assure a nosological independence for these cases. He attempted to establish that they showed, in contrast to the classical form, a *series of important differences in symp-*

This occurred in Cornil's and Kocher's cases Of the medullary carcinoma investigated by Hanig the more peripheral parts contained small colloid globules within the cellular matrix. The metastatic cancerous tumor in Harmer's case showed, in places, a glandular structure with colloid-filled spaces, and in Lowy's second case the pronounced glandular structure of some parts, with scanty colloid in the thyroid gland tumor as well as in the metastases, was emphasized

It is not impossible that in exceptional cases cancerous thyroid tumors and their metastases can cause changes in organisms analogous to the otherwise benign, diffuse hyperplasia of these glands. Highly instructive in this regard is v Eiselsberg's observation[1]

After extirpation of a carcinoma which occupied the larger part of the thyroid gland the manifestations of *cachexia strumipriva* appeared. These improved when a metastasis had formed in the breastbone. After its excision signs of cachexia recurred. When we see that a cancerous metastasis can take over the functional activity of the parent organ up to a certain degree, we can understand that it might be able, by an altered functional activity in a certain direction, to bring about Basedow's disease signs We have seen that, in the cases of Harmer, v. Stejskal and Lowy, the Basedow's disease signs appeared only after the appearance of the metastases It is also noteworthy that in so extensive a cancerous degeneration of the thyroid gland as that of Glunet's case, pronounced Basedow's disease signs arose and not manifestations of *cachexia strumipriva*. Other glands of internal secretion seem to have participated here vicariously to a certain degree

§245. Among the disease forms associated under the title of thyrotoxic goiter heart, goiter and cardiovascular signs predominate. In another very extensive group of incompletely developed cases the nervous signs stand out more prominently. The thyroid enlargement is sometimes only slight, or only discernible upon special examination Besides continuing or recurrent tachycardia and palpitation, there is characteristic tremor, general nervousness, psychic and motor restlessness, rapid fatigue, sleeplessness, and loss of strength, all of which form the combined symptom complex of the case history Such patients are often treated for neurasthenia without noticeable success or are sent to spas on account of anemia It can not be denied that such cases sometimes remain obscure for a while and that they can cause considerable diagnostic difficulty. It is here, therefore, that the presence or occasional occurrence of certain conspicuous secondary signs, the results of blood tests, and the testing of the respiratory quotient is of decisive significance

Sometimes one or another of the eye signs such as a wide opening of the lid aperture is discernible; more rarely also a slight degree of protrusion of the eyes The patients often suffer from localized or general outbreaks

[1] Archiv fur klinische Chirurgie XLVIII, p. 488.

In 8 cases palpitation or tendency to palpitation had been present since childhood, or for a number of years before the first of the other signs appeared nervousness, tremor, "enlargement of the eyes", and swelling of the neck First one sign then the other became more conspicuous. In 2 cases enlargement of the neck, palpitation and tremor arose only at the menopause In a few cases palpitations preceded the appearance of a discernible goiter

If one wishes to use a special name to designate that group of cases of rudimentary development in which the nervous signs stand out as significant there would be no objection to the name of *Basedowoid* In like manner, we associate *a definite concept with the terms goiter heart* and *struma basedowificata*. Only, these cases should not be put up as specially opposed to the classical form and one must keep in mind that real hysterical and neurasthenic signs are not of the essence of the disease, but, rather, that they represent a complication

F. Chvostek (3219) would distinguish still another group of cases from the rudimentary form of Basedow's disease He combines them under the name of cardiovascular neuroses They occur predominantly among persons of middle age with a hereditary neuropathic predisposition and nervous *manifestations which have been present from early youth They develop* from one's work or following mental excitement etc and appear predominantly in the circulatory system and vasomotor system Reddening of the face, dermographia, sweating, tachycardia, and lability of the pulse rate are the common signs *These do not occur in association with dilatation of* the heart The heart shows signs of irritability without becoming easily exhausted. The pulse difference when in a prone or standing position is exaggerated The pulse sometimes exhibits slight arrhythmia. The carotids pulsate Sometimes, one observes marked pulsation in the abdominal aorta

Chvostek himself clings to the diagnosis of a *cardiovascular neurosis* when there is a fine or choreiform tremor or a wide gape of the palpebral fissure or Mobius sign, or even a small goiter, and he wants to separate these states completely from Basedow's disease as having nothing to do *with a functional disturbance of the thyroid gland It does not seem always* feasible to agree with him It is, however, correct that the unusually great lability and irritability of the heart, and the alternations of an almost normal pulse rate with periods of great rapidity and arrythmia, are foreign to the typical pattern of Basedow's *disease*, yet we have seen that these manifestations do occur occasionally in some cases in which the total disease picture leaves no room for doubting the diagnosis of Basedow's disease (see §238 above)

§246. A small group of non-typical cases remains in which the cardiovascular as well as the nervous signs are more or less hidden or slight while the eye signs attract the most attention Exophthalmia and the lid signs,

tomology and development such that one was justified in using a special name, *Basedowoid*, for them He believed that *Basedowoid* could be explained by the combination of goiter heart with an original, degenerative, neuropathic predisposition Stern also believed that, from the "classic form" a genuine or pure Basedow's disease and a degenerative form may be derived. The latter arises from a complication of the former by a hereditary, degenerative disposition This separation seems to me arbitrary; the proposed distinguishing characteristics were by no means significant. Little as we know about the nature of the thyrotoxic damage, this much has been established: we are dealing with a nerve poison which damages the central as well as certain peripheral areas of the nervous system. It is clear that when this poison acts upon an individual with a labile nervous system or one with a degenerative, neuropathic disposition, the signs from the nervous system will stand out more actively, or indeed dominate the disease pattern. We have discussed these relationships in describing the psychoses which occur in Basedow's disease (see §161 above). Quite similar conditions occur in other diseases, without the necessity of dividing them into two groups. Actual "neurasthenic hysterical states", however, should be considered as complications not essential to the disease itself, this, too, we have attempted to demonstrate clearly above (see §145 and §146), they certainly can not offer a cause for a separation Actually, all the characteristics which distinguish the genuine from the degenerative Basedow's disease become inconclusive as they derive from the age of the patient, the hereditary tendency, the more acute or chronic course of the disease, the condition of the tremor, etc And, finally, concerning the myopia, which is rare in true Basedow's disease, but frequent in the degenerative form and the *Basedowoid*, I need only to refer to what has been said in §78 above There is hardly any extensive amount of Basedow's disease material in existence, including all the various forms of the disease, which has been ophthalmologically tested so thoroughly as mine. Among 103 cases 11 had myopia and 10 simple astigmatism Most of them were only slightly nearsighted, 0.5–2.75 D; only 3 were over 10 D. The latter category included a man of 39 *who had been treated as a neurasthenic before the nature of the* Basedow's disease was recognized This appeared to be within the pattern which would correspond to Stern's *Basedowoid* Among those of a lower grade was a 55 year old woman with degenerative neuropathic predisposition and a number of signs to be regarded as a complicated hysteria. All the other cases showed the pattern of a typical, uncomplicated Basedow's disease.

Stern's explanation of *Basedowoid* from the combination of goiter heart and an original neuropathic predisposition cannot hold good. In a large number of cases, rather carefully described by him, 47 *Basedowoid* cases lacked a previous history of a simple goiter so characteristic for goiter heart prior to the appearance of the thyrotoxic symptoms

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§246. A small group of non-typical cases remains in which the cardiovascular as well as the nervous signs are more or less hidden or slight while the eye signs attract the most attention. Exophthalmia and the lid signs,

or only the latter, sometimes developed on only one side, sometimes lacrimation is the most conspicuous sign for a time or during the entire period of observation These are also the complaints which first influence the patient to consult a doctor. Little attention may have been given to other signs which were also present, such as palpitation, nervousness, and perspiration. An exact, purposive, examination often brings to light a series of other signs: tachycardia, pulsation of the cervical arteries, fullness of the anterior neck region, and delicate tremor of the hands. In some of these cases the *symptom complex becomes complete in the course of the observation.*

Thus, the peculiar appearance of the eyes of a young woman accompanying a relative to the consultation room attracted the attention of S. Shell (737). When he examined her more closely he found a marked retraction of the upper lids on both sides, v Graefe's sign, and evidence of exophthalmia No swelling of the thyroid gland was discernible, cardiac signs were absent In the subsequent course the missing disease signs appeared Gifford's case was similar (see §53 above). The case of J B Nias (1063) referred to earlier (§119) also belongs here, this case never reached the stage of the complete symptom complex A man of 34 whom Cerised (Monthus 3004) observed in the clinic of Lapersonne had a retraction of the right upper eyelid which was conspicuous at his first visit Five months later v Graefe's sign could be demonstrated He also developed a moderate tachycardia, even while resting, and a slight tremor of the hands.

Sometimes, among these non-typical cases, the absent signs do not appear even after long periods of observation Sometimes the symptoms which are present regress again under treatment.

Quite a series of cases belonging here have been brought to our attention in the earlier discussion of the lid signs (§47, see also §81).

Diagnostic errors occur easily if in such cases a careful examination is omitted, as for instance, in cases with unilateral lid signs. The pertinent literature shows may examples of this (see also §268, below)

In a few cases in which, except for the lid signs, only a few not very characteristic signs were present, the observation covered only a brief period, and it remains doubtful whether the interpretation of the case as an *abortive form of Basedow's disease is admissible or not*

In this connection one may recall an observation of S Snell (737) concerning a 36 year old worker in a coal mine This patient had a nystagmus, to which earlier reference has been made (§105) The classification of a case of F Semon (863), reported to the Clinical Society of London, as a unilateral and incompletely developed Basedow's disease is somewhat uncertain In the case of a 30 year old man, a marked retraction of the right upper eyelid and v Graefe's sign followed a nasal operation

the pulse, about 80 beats per minute was evident When Semon undertook additional operations after one or two months, the pulse rate increased to 110 and more and for over two months remained at this rate No enlargement of the thyroid gland was discernible during the entire period of observation A similar situation was illustrated by two cases of B Holz (2514) He considered this an incomplete form of Basedow's disease The patients, 7 year old boys in both cases, showed exophthalmia on both sides There was a marked widening of the palpebral fissure and v Graefe's sign was more pronounced on the right than on the left Heart action was normal, no enlargement of the thyroid gland discernible Furthermore, signs were present pointing to adenoid growths in the nasal cavity The boys were pale and for their age not well developed, one of them was mentally retarded, the other alert Ten and fourteen days respectively after the removal of the adenoid growths exophthalmia and lid signs had disappeared In one of them, two years later, the same manifestations reappeared Radical removal of the tonsils brought a permanent cure

A few difficulties in diagnostic interpretation are encountered in the following cases, Passler (1362) found slight exophthalmia, widening of the lid aperture, and v Graefe's sign in the case of a 20 year old male student The pulse fluctuated between 80 and 120, but it was not certain whether the rise in the pulse rate should not be attributed to excessive use of alcoholic beverages Subjective difficulties of the heart were absent Furthermore, for years he had perspired heavily Flatau (1963) reported a woman of 52 who had exophthalmia, distinct lid signs and who suffered from mental excitability, but no signs of Basedow's disease

A 22 year old, sturdily built but somewhat anemic miner's daughter was observed by Vossius (1387) The right palpebral fissures was noticeably wide and the right lid remained far back during blinking On the other hand, the left palpebral fissure was narrowed by a slight ptosis and the left upper lid moved downward in the normal way Involuntary blinking occurred infrequently The slight prominence of the right eyeball was perhaps due to the strong retraction of the upper lid (see §43 above) In normal lateral eye movements a convergence of the two eyes had become "almost entirely impossible" Heart action was quiet and regular Goiter could not be demonstrated The patient was weary and easily depressed Eight months later her general condition seemed to be improved, both lid apertures were now of equal size In addition there are still a few other cases among those discussed (§47 above) which are diagnostically uncertain, as for example Passler's observation of a 62 year old farmer, that of Wilbrand and Saenger (2033) of a 39 year old woman, Awerbach's (2601) case and perhaps still others In certain cases in which lid signs were plainly evident, as, for instance, in Albrand's case (1086), (see §56 above), there is hardly any doubt that they should be considered incompletely developed cases of Basedow's disease

The Course of Basedow's Disease

§247. The course of the largest majority of cases is chronic The disease, fluctuating repeatedly, drags along for years Sometimes these fluctuations are rather considerable, so that shorter or longer periods of comparative well-being alternate with those of more or less severe illness

The rapid pulse, the palpitation, the accelerated breathing, the tremor, the mental excitability, and the symptoms connected with the digestive system and the general state of nutrition not infrequently vary conspicu-

ously. One or the other of the signs may disappear entirely during remission, so that the symptom complex comes to light more or less completely only during the exacerbation.

In many cases these exacerbations occur so suddenly and for such a relatively short time that one is justified in calling them attacks. These we have already described before (see §5 above). The occurrence of paroxysms of palpitation with distressing sensations of anxiety and marked acceleration of the pulse is usually accompanied by simultaneous exacerbation of other disease manifestations. Sometimes, during such attacks, the neck also increases in circumference and the eyes protrude more. Also, there may be a rise in body temperature A copious nosebleed in the cases of many patients brings the attack to an end (Trousseau 219). Murray (2213) and Rollestone (2226) explained the occurrence of such paroxysms or crises as a peculiar feature of Basedow's disease.

More rarely the development of the disease is completed by means of periodic advances The signs increase with each attack. The remissions become shorter, until a certain high point is reached.

Usually the fluctuations in the course of Basedow's disease are less conspicuous The phases of regression and improvement change gradually from one into the other and they each last for a fairly long time. Exacerbations are not infrequently brought on by mental excitement, a relatively slight bodily exertion, by menstruation or pregnancy, or by some other such influence. *In many cases these causes are evident*

Among Kocher's (2197) 80 cases there were 7 with especially conspicuous fluctuations A woman of 22, during two and a half years, and a woman of 54 during a three

adaptation to the changed mechanical requirements of an altered bodily position was insufficient as a result of disturbed vascular innervation R Stern mentioned that, in several cases assembled as *Basedowoid* (see §245 above), a kind of periodicity of the ailment was discernible A woman stated that for 20 years she had always been well in the spring and summer and ill in the winter

§248. Sometimes, in the course of a mild or moderately severe Basedow's disease we see a sudden reverse with an alarming exacerbation of all the disease signs Or a new serious symptom may appear, such as vomiting, diarrhea, a temperature rise, or delirium The disease passes over from the chronic into the acute stage. Usually there is a definite causal factor, sudden fright or any other violent emotional shock, overexertion, strong sexual excitement, an operation, a mild infectious disease or an attack of gastroenteritis.

This acute phase can either pass off and make way for a further continuation of the course or it may lead to death within a few weeks or months. In severe cases of Basedow's disease acute exacerbation with an increase in pulse rate up to 150 and over, shortness of breath, rise in temperature, continuous vomiting, great mental excitement, jactation, delirium, or deep depression occurs not infrequently during the final days before death

Accounts of such cases have been given by Drummond (702), Foxwell (1433 and 1571), Hezel (1114), Roper (1911, 1, 2, 3, 4, and 5), Klein (2393 see also §129 above), Lawrence Humphry (2518, 1 case) and others

In the case of a 27 year old servant girl observed by Merklen (494), after a Basedow's disease of 6 years duration and following temporary improvement during a long stay at the seashore, acute manifestations arose, including headache, violent palpitation, reddening of the face, a temperature rise up to 39° or 40°, *taches cérébrales*, albumenuria, and epileptiform convulsions (see §121 above) The goiter became enlarged and developed a distinct *bruit* and pulsation synchronous with the pulse There was a high degree of exophthalmos and a permanent enlargement of the pupils which, upon exposure to light, contracted only slowly and incompletely Following the administration of digitalis and bromide of potash the epileptiform attacks as well as the irregularities of the heart beat ceased The albumen disappeared from the urine From the eighteenth day on the temperature was normal The other signs gradually returned to their earlier condition, and the patient felt fairly well

Another case which belongs here was contributed by G v Voss (2352) A woman of 22 had suffered from Basedow's disease for some time Following gradual improvement a sudden reverse set in The pulse rate rose to 132, vomiting occurred and became more and more frequent, and weight declined rapidly Finally, the patient lay with eyes half-closed and slightly dazed She lost control of her functions, and vomited continually Her pulse became irregular At night she became delirious and jumped up She presented the picture of a severe, acute intoxication Gradually consciousness returned, and with increasing improvement her weight increased After a three months stay in the country the patient was so much improved that she was able to resume work Five months later a worse relapse occurred complicated by the varying eye-muscle paralysis discussed above (§127)

A woman observed by W Gilman Thompson (2773) had a slowly increasing goiter, mild Basedow's disease signs for twelve years, and distinct exophthalmos An extremely severe exacerbation of the signs was set off suddenly by an acute tonsilitis Heart action was unusually forceful The heart showed great dilatation and loud sounds at the apex and base Following this inflammation of the tonsils her temperature rose to 40°, although, after treatment with Rogers' serum the woman was cured in 14 months except for a slight exophthalmos and a small swelling of the thyroid gland The cardiac enlargement and loud heart sounds were completely gone

A 32 year old woman had always been somewhat irritable, but otherwise healthy She had suffered from a slight disability caused by Basedow's disease for three years Eger (464) reports that, following a violent emotional disturbance, an acute exacerbation and severe disease began with obstinate vomiting Following the development of emaciation, uncontrollable vomiting, and an icteric skin color, death came in the sixth week after the beginning of the acute manifestations (see §173 and §175 above)

A 25 year old girl whom Lawrence Humphry (2518) observed had suffered from Basedow's disease for four years Rest and internal treatment improved this condi-

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Among Kocher's (2197) 80 cases there were 7 with especially conspicuous fluctuations A woman of 22, during two and a half years, and a woman of 54 during a three year course, improved during the winter Kocher also observed, in a very large number of his cases, a regression in the morning among those who either did or did not suffer from sleeplessness He is of the opinion that in the cases of such patients, adaptation to the changed mechanical requirements of an altered bodily position was insufficient as a result of disturbed vascular innervation R Stern mentioned that, in several cases assembled as *Basedowoid* (see §245 above), a kind of periodicity of the ailment was discernible A woman stated *that for 20 years she had always been* well in the spring and summer and ill in the winter

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An 18 year old girl, whose interesting case history is contributed by J Rogers (273a), had noticed a soft swelling on her neck Thyroid tablets were prescribed A month later the patient suffered a fainting attack and the symptoms of thyroidism appeared These symptoms disappeared, after discontinuance of the thyroid medication But after an inflammation of the tonsils they appeared again Then all disease signs once more disappeared except the soft goiter After a few months they appeared again, and once more improvement followed After a stomach catarrh resulting from an error in diet, the symptoms of a severe Basedow's disease suddenly appeared, with a pulse of 200, difficult breathing, 30 or 40 breaths per minute, violent headache, a high degree of nervous restlessness and then stupor Finally a rightsided, incomplete hemiplegia and Cheyne Stokes respiration developed Breathing then ceased entirely This death occurred a little over a week after the appearance of the acute symptoms

R Breuer reports the case of a woman with a slowly developing goiter with mild Basedow's disease signs (probably the evidences of thyrotoxic goiter heart) (2153) "A severe, almost fatal thyroidism" arose following the use of iodine in relatively small amounts

A woman of 53 treated by H Brooks Wells (2597) had a moderate thyroid enlargement for some time, and suffered from the symptoms of goiter heart Following a uterine curettage for an endometrial disorder, a high degree of nervous excitement, increase of the tremor, and distinct enlargement of the thyroid gland accompanied the appearance of vascular signs including a rise in the pulse rate to 150 There also was a temperature elevation to 40° and over This precarious situation lasted three weeks, then an improvement took place slowly Medication was ineffectual

A woman of 35, reported by Audebert (2600), had suffered from certain Basedow's disease signs since her first pregnancy In her second pregnancy she developed albumenuria, edema, and difficult breathing Toward the end of eight months the signs suddenly became very severe With an increase of the albumenuria, the appearance of anasarca and marked dyspnoea the tachycardia increased, as did the circumference of the goiter Tremor and exophthalmia also appeared After the induction of an abortion all the signs improved After five months the woman was nearly cured

§249. It does happen not infrequently that a new flare-up of the disease occurs even after great improvement or apparent cure Sometimes, these relapses appear in a most severe form, and, within a short time, result in death When the relapses occur again and again they rob the patients, even those with less severe forms of the disease, of any enjoyment of life and make them into chronic invalids

According to Kocher's experience (2197) relapse is almost the rule with internal and dietetic treatment of Basedow's disease Even if consistent adherence to the established rules of procedure result in considerable improvement, a sudden event as, for instance, violent fright, or pregnancy, or infectious disease, may produce a severe relapse.

In the case of a 31 year old female patient, reported by Kocher (2197), treatment with medications and repeated fresh air and water treatments brought about a great improvement such that the woman could carry on her household duties and give birth to two children without harming herself After a number of years, following a great shock caused by her mother's sudden death, a sudden recrudescence of all

tion She returned to work half a year later The symptoms appeared again with renewed violence Obstinate vomiting began, and the patient had to be fed *per rectum.* After brief improvement she became restless, excited, and sleepless, she vomited ceaselessly, and was short of breath The pulse could not be counted. Suddenly, the patient developed a severe pain in the left leg This leg became cold, and a short time afterward the patient died of cardiac paralysis

An instructive case in which acute exacerbation occurred shortly after the onset of the disease was observed by Pässler (2559), a 23 year old farmer's daughter who came from a healthy family and had never been seriously ill, although she had had a small goiter for a long time In a few months a gradual change of her personality was noticed She showed nervous restlessness, emaciation, lack of energy, weakness of the legs, protruding eyes, and a tremor Following too much dancing at an autumn festival the signs increased to the stage of an extremely severe illness. The patient became unconscious, and suffered from extreme breathlessness; the skin of the face was flushed, the pulse was rapid (120 to 135) and weak Intense excitement alternated with anxiety states At times vomiting occurred Notwithstanding these severe symptoms the operation on the goiter was undertaken during anaesthesia. It was performed without serious bleeding. Death followed four hours later (about seventeen days after the beginning of the acute exacerbation).

Another case is reported by Schubert (2880) A girl of 19, following a several weeks course of moderately severe Basedow's disease, had a sudden exacerbation followed by death six days later

A man of 44 observed by Mouriquand and Bouchut (3005) had an arthralgia complicated by a typical Basedow's disease which at first seemed to be running a favorable course With the outbreak of icterus and copious vomiting of bile, the disease took on a severe, acute course and ended in death

Even administration of thyroid-gland tablets can cause a Basedow's disease which is at a standstill, or which is improving, to relapse acutely.

A perfect case of this sort is reported by Auld (1168) A girl of 26 with typical but not severe Basedow's disease was steadily improving After oral Burroughs and Wellcome thyroid tablets in very moderate doses (only 1 tablet every 3 days, in the third week 2 tablets daily) the slight exophthalmia rapidly became greater, thyroid-enlargement progressed, pulse rate increased from 99 to 138, and temperature rose above 38°, the patient suffered from diarrhea, perspired profusely, felt ill, and became progressively weaker

Mild forms of the disease in the form of thyrotoxic goiter heart (see §242 above) may be transformed into a severe acute form of Basedow's disease by use of thyroid tablets or by some other, relatively slight, means

A 24 year old girl, observed by M V Ball (2453) for three or four years had suffered from a small goiter, tachycardia, palpitation, and pulsation of the cervical arteries On account of this the patient took thyroid extract for the period of one year Thereafter a staring expression, a wide gape of the lid aperture, and tremor was noticed Loss of appetite, vomiting, diarrhea, and, soon afterward, great nervous restlessness arose The patient became emaciated and displayed purpuric spots on the extremities An increase in temperature, pulse rate of 200 and respiratory rate of 70 per minute preceded death in coma

A 26 year old woman from a healthy family was reported by Roper (1911, 5th case) She had a typical Basedow's disease which was attributed to too much dancing After visits to spas and fresh air resorts the improvement was so considerable that the young woman was able to undertake strenuous mountain climbing during spring and summer A sudden relapse occurred following these adventures and some excitement during the last climbing expedition, when they were surprised by a heavy shower After many slight fluctuations all the signs increased in intensity, the temperature rose to 38 6°, the excitement and weakness continued to increase, and five months later sudden death occurred following a severe relapse, about five years after the first outbreak of the disease

A 23 year old Russian lady suffered greatly from palpitation and occasional diarrhea and became greatly emaciated following influenza In Badenweiler, where she was sent on account of "affection of the lung apex" Thorbecke (2589) recognized a severe Basedow's disease During repeated attacks of diarrhea her temperature rose to 38° or 38 5° At other times no fever was present Suitable treatment resulted in very noticeable improvement Three or four months after the return to St Petersburg she suffered a severe relapse with periodic diarrhea, fever, progressive emaciation, a high degree of nervousness and mental excitability, a marked tremor and a powerful pulsation of the carotids and the aorta The goiter had nearly disappeared, and the exophthalmos was not much altered Finally, bloody vomiting, bloody diarrhea and irregular and unaccountable pulse preceded death from heart failure about three months after the beginning of the relapse

In the cases of H Stern (2238), Salomon (2432) and Osterwald (1768) a relapse of Basedow's disease complicated by diabetes occurred following almost complete cure after 3, 10, and 20 years, respectively (see §232 above) In the latter case a remission of both diseases occurred In the other 2, death came five months after the beginning of the relapse

§250. In a majority of cases the onset of Basedow's disease is gradual and inconspicuous with hardly noticeable signs easily overlooked by the patient or, at least, not always sufficient to lead him to seek out a doctor If one pursues the subject carefully enough it is often possible to ascertain that a small swelling on the throat, frequent nervousness, altered moods, pallor of skin, and fatigue or hot flushes and perspiration have been present for some time Even when the doctor is consulted these symptoms will frequently be interpreted in some other way The whole grouping will be encountered not only in individuals with a degenerative neuropathic predisposition, as R. Stern (3060) believed he must assume in the material which he studied, but also in those who were previously quite healthy and did not have any hereditary predisposition One could designate this initial stage as the period of prodroma or latency (Renaut, 1372) The beginning of the disease in such cases can, therefore, hardly be determined exactly The patients are inclined to date the onset from the time when, sooner or later, conspicuous or disturbing signs appeared, or from any event which had impressed itself upon their memory as the beginning of a rapid development of the symptom complex It is not unusual to find a short stage of latency with only slightly developed disease signs in cases in which the whole

the Basedow's disease signs occurred, including enlargement of the thyroid gland. Then the heartbeat suddenly became unusually rapid, and tonic convulsions were followed by death

Experience has shown that surgical treatment of Basedow's disease does not exclude the possibility of relapses. Kocher believes that they occur mainly when not enough of the thyroid is removed by the operation.

Krong (2700) *states that among his 106 cases, of which only 10 were* severe, only 2 remained entirely free of relapses for the next nine to eleven years Both Kiehl (2982), and Fr. Schultze (3049) emphasize the unpredictable nature of Basedow's disease. R v. Hosslin (3140) often observed that, with internal medical and physical dietetic treatment, a relapse occurred after apparent cure. Přibram (2727) on the basis of his experience is very optimistic about the possibilities of curing Basedow's disease by internal medical treatment (see §258 below). Among others, he had one very severe case which improved very considerably within a few months. But a relapse occurred a few years later

Konigstein (3145) reported 3 cases of repeated relapses. In all these cases the onset and the course of the single phases of the disease were acute.

A young girl had an acute attack of severe Basedow's disease Because of rapidly progressing emaciation her condition became critical Almost as rapidly a turn for the better followed All signs disappeared. The loss of weight was overcompensated. Within a few months the girl enjoyed the best of health Then followed, without evident cause, a sudden return of the disease in a still more violent form She became as thin as a skeleton and extremely decrepit, abscesses developed on both corneas, then again, suddenly, a change to complete well-being appeared, a tendency to obesity, and, after a few months, a return to her former weight Then came a third attack, but this one took a milder course After that she remained in continued good health Only a slight exophthalmos remained from the former illness The second case was more severe and was complicated by a psychosis During the second period of emaciation heart failure caused death. The third case withdrew from observation after the completion of the second cycle.

Other cases in which severe relapses occurred after periods of well-being lasting several years are reported by Gaill (544), Stiller (793), Johnston (1093), Mannheim (1222, 29th observation), Paterson (1232), Baginski (1401, a 12 year old girl), H. Schulz (2118) and a few others.

In a few cases the recurring disease, taking an acute form, ended fatally.

We have just learned of such an acute case observed by Königstein One of Dinkler's (1711) patients developed typical Basedow's disease in her forty-first year After a duration of about half a year she was completely cured in a rather short time But only a few weeks after her return to the city periodic vomiting began (see §173). In addition to definite signs of Basedow's disease she also developed nervous, bulbar, and mental disturbances (see §131), a temperature rise to 39°, and an increase of the pulse rate to 200 Death occurred about 3 months after the beginning of the relapse.

plex suddenly developed, together with a nosebleed which lasted all night and a cessation of the menses which had just begun

Roth (341) observed a similar acute onset of Basedow's disease in the case of a 44 year old woman after the sudden cessation, from no known cause, of menses, which up to that time had been regular A male patient of 21 seen by A v Graefe (192) and Förster (355) developed the disease in its entirety in a few days following a forced coitus carried on against energetic resistance by the other party The act was finally completed following half an hour of continued exertion Exhausted in the extreme, and bathed in sweat, the young man attempted to regain his strength with a few glasses of madeira wine immediately afterwards The same night he developed severe palpitation The next morning he felt exhausted, and noticed a change in the expression of the eyes Twenty-four hours later the eyes were distinctly exophthalmic During the next two hours this had progressed to the startling degree which was displayed at the time of the examination Seeligmuller (531) made the observation that a youthful nurse, who erroneously had given a child a dose of atropine solution, developed an acute episode of Basedow's disease during her anxiety over the life of the child

Potain (498), in two cases, saw a very acute onset of the disease directly after a violent outbreak of anger Charcot (113) observed an 18 year old girl with hereditary tendency In childhood this girl had shown a slight hesitation in her movements and slight tremor of the hands The typical symptom complex developed rapidly a few days after her wedding A hysterical girl of 18 had an acute onset directly after a stormy family quarrel involving a drunken father (1816) Mathieu (922) mentioned briefly a severe case of Basedow's disease developed by a young woman immediately after her wedding During the first night she was much excited, and developed severe palpitation which continued afterward A few days later the other signs appeared Winternitz (873) observed an acute outbreak in the case of a man who had just had an emotional shock Two hours afterward the eyes protruded, the thyroid gland enlarged, there was a rapid pulsation in the neck, and palpitation with a distinct enlargement of the right ventricle Nothing is known of the further course A previously healthy 12 year old girl with no hereditary tendency was reported by Rahel Hirsch (3135) She had attacks of heart palpitation, anxiety, and sleeplessness, directly following excitement caused by her being taken to a morgue At the same time the mother noticed a strong protrusion of the eyes and a swelling on the throat The further progress of the disease was chronic (see also §285 below) Ch E Renault reported the case of a 19 year old girl (930) A few days after violent excitement because of the failure in a test, all the signs of Basedow's disease and a number of secondary signs appeared Then followed an obstinate course with intervals of slight improvement In a case of Corkhill (1096), a woman of 32 suffered an acute onset of Basedow's disease soon followed by a transition into myxedema (see §221, above) Přibram (1368 and 2727) reported the case of an 18 year old girl who had a hereditary neuropathic predisposition, but who had remained well previously After diving into the water in a swimming school she remained under the water for a rather long time and was taken out unconscious Immediately following this episode the entire symptom complex of an extremely violent Basedow's disease developed with the utmost rapidity The patient remained in the clinic for observation only a short time She was said to have died some time after her discharge In the case of a 24 year old woman without any hereditary tendency, the symptom complex of Basedow's disease developed, as reported by Low (1611), in a rather acute form after she had been thrown from a frightened horse The further course was chronic At the time of

Basedow's disease syndrome develops in an acute form. Mobius (1478 and 2717) probably goes too far when he says that the onset of Basedow's disease is always insidious. There are certainly cases in which the full development of Basedow's disease into the usual severe disease pattern occurs in a really violent manner (see §252 and §253 below).

Among 20 cases the detailed histories of which were available to Gillespie Beardsley (2907) the signs developed suddenly in only 2 Of the other 18, 12 had been treated over varying intervals for nervousness or gastric disturbances, and 6 for heart ailments

In 27 among 32 cases operated upon by Klemm (2976) for Basedow's disease the disease started quite gradually In 5 cases an acute onset was specifically mentioned A patient was attacked by violent palpitation and anxiety while on a journey. The other signs of Basedow's disease followed in rapid succession. The further course was chronic

In quite a few cases only the onset of the disease is more or less acute After a shorter or longer interval at this stage, the illness drags along with partial remission of the disease signs Once the disease has entered a chronic state or a period of tolerance (Renaut), this may continue for years with numerous fluctuations.

In another group of cases, fortunately not very extensive, the disease takes the pattern of a severe poisoning, and follows a wholly acute and malignant course ending in death after a few weeks or months. The signs are essentially those described briefly above (§248). Gilman Thompson (2773) called attention to the fact that cases of this sort suggest an *endocarditis maligna* or a so-called cryptogenetic septicemia, especially when, as often happens, the goiter is only small and the exophthalmia not conspicuous By exceptionally violent heart action and toxic damage to the heart muscle itself it leads to acute cardiac dilatation and heart murmurs (see §10 and §11 above).

Still more rare are the cases in which, after acute onset, an equally rapid turn for the better occurs in a relatively short time, and the disease ends not in the chronic state, but in complete recovery This has been observed even in cases which followed the pattern of an extremely severe illness *(see §253 below). Sometimes in this group of cases the disease is mild or* does not reach full development of the symptom complex at all.

§251. We shall now present a few especially striking examples in which Basedow's disease developed in acute form. Whether or not one or the other of these cases was preceded by a latent stage cannot be determined from the descriptions.

Trousseau (166) and Peter (160) reported a woman who, in her fifty-fifth year, spent a night weeping over the death of her father At that time the symptom com-

ment of the thyroid gland and the onset of the other signs of Basedow's disease The patient died about four months after the acute outbreak There had been an elevation of body temperature and a marked acceleration of pulse and respiratory rate during convalescence from a pneumonitis of the right lung Among 12 cases fully described, there is 1 which is acute Hector Mackenzie (918) found no acute cases of Basedow's disease among the 30 cases which he had an opportunity to study Among 17 cases reported by Ditisheim, 1 took an acute lethal course Among 89 cases of Basedow's disease which came under his observation at the Leipsic Medical Clinic within 10 years, Roper (1011) found 3 with a sub-acute course which ended in death (cases I, II and IV) Kocher (2197) had observed, among 80 cases, 5 with an acute course Complete cure was achieved in all of them (see below) Kroug (2700) noted among his 106 cases 3 severe and acute Rogers (2736) stated that he had seen 1 case with the acute form of Basedow's disease Frank Billings (2806) noted 12 among 61. Among my own 103 observations 1 case of acute Basedow's disease is noted

Two cases among children took an acute course which, after 10 and 14 weeks respectively, ended in death Schwekendiek (569) reports the case of a child of 2½ years, and Ditisheim (1293) a boy of 13 (see §296 below)

W. Mackenzie (49 and 57, 28th observation) reported a 16 year old boy who had participated in all kinds of sports A sudden outbreak of Basedow's disease with all of its signs was said to have followed catching a cold on a railway journey The boy died after a few days N L Rey (302) reports briefly that a 19 year old girl, after childbirth, developed a severe acute Basedow's disease which, at the end of a week, led to her death A 24 year old girl with serious predisposition was observed by Savage (568) Basedow's disease was complicated by manic-depressive insanity, and ended fatally after six weeks during manic excitement with exhausting diarrhea A girl of 18 under treatment by Clarke (695) free from any hereditary predisposition had always been healthy, until a slight swelling appeared on her throat and she began to have frequent headaches During this interval the girl had one attack of palpitation After two months this attack was followed by another Then followed a rapid onset of Basedow's disease with diarrhea and vomiting Death occurred six weeks after the outbreak of the acute symptoms In a case described by Hendrick Lloyd (778), that of a 30 year old woman, the course of the disease was unusually rapid The illness began with violent emesis and diarrhea, it ended on the third day by death from heart failure Six months earlier she was said to have had a brief illness, perhaps of similar nature Equally rapid was the course observed by Chevalier (852) A 30 year old man was free from hereditary predisposition and had previously been healthy The disease began with a violent headache Two days later, after excitement, palpitation and diarrhea occurred Some days afterward the thyroid gland became enlarged and the eyes protruded The heart became irregular, with loud sounds, and the pulse became almost uncountable There was pronounced tremor Then epileptic attacks began (see §120 above) and bulbar signs appeared (see §127 above) Death occurred during an epileptic attack after the sixth day of the illness It had been noticed some time before that the patient's naturally gentle disposition had changed into an excitable one, inclined to outbreaks of anger E Reymond (1143) observed a Basedow's disease with a very acute course A woman of 45 had a tremor for one and a half years following a shock But otherwise she had no signs indicating Basedow's disease When this woman became excited because the life of her daughter was endangered by childbed fever, the symptoms of Basedow's disease developed rapidly Death occurred 2 weeks later following a rise in temperature, a continual shaking of the entire body, uncontrollable vomiting, and mental confusion Death occurred

the observation the illness had already lasted three years A 38 year old woman under treatment by Berthels (2616) had severe palpitation, headache, and tremor directly after a stormy voyage during which she was seasick and hung over the rail in constant fear for her life. A swelling arose on her throat She rapidly became emaciated. In spite of careful treatment the condition continued to grow worse until an operation on the left thyroid lobe, ten weeks after the onset, brought considerable improvement A complete cure was achieved fourteen months later (see §195 above). Two sisters, one of them 17 and the other 23, as reported by Mayzele (1622), both met with an accident at the same time, while bicycling They were greatly frightened and excited over it A violent tremor began which neither had had before The older girl had a palpitation which she had not had previously. The examination on the seventh day after the accident showed the clear picture of Basedow's disease in both, but in a mild form The further course was chronic Harland (1970) reported two soldiers who rapidly developed Basedow's disease during the Boer Expedition In one case it was the consequence of a slight head wound during the Battle of Eland The wound itself healed quite well, the other soldier, who was never wounded, developed the disease during convalescence following dysentery

Hammerschmidt (2187) described as acute Basedow's disease the case of a recruit Following the recoil of his weapon, which he shot for the first time with a blank cartridge, the fully delineated Basedow's disease picture developed within six weeks It continued with moderate severity, unaffected by therapy The patient had a hereditary neurotic predisposition He had previously experienced occasional palpitations. It is possible that a short latent period had occurred and that fear of the shooting had furnished the final factor for the rapid development of the symptom complex Remlinger (2731) observed a 29 year old Turkish soldier who had no neuropathic predisposition and who was of a calm temperament The outbreak of Basedow's disease with a swelling of the thyroid gland began a few days after an attack by a mad dog had caused him to become extremely excited

In 3 among 80 of Kocher's (2197) cases the disease developed in an acute fashion and then took a chronic course

In J Griffith's (1728) case, that of a 21 year old girl, the development of the symptom complex was rapid, and abscesses on both corneas appeared very soon (see §91 above) Le Gendre (2200) reported an "almost sudden" development of the typical disease picture in the case of a 37 year old woman In a case of Hendriessen (2838) the disease began suddenly with a temperature rise to 41°, general depression, nosebleed, and diarrhea A few weeks later goiter, exophthalmia, and tachycardia appeared

§252. Numerous cases are recorded in which development and course take place in a relatively short time, ending in death Nevertheless, we must maintain that this behavior of the disease is unusual and, actually, exceptional It is just because the alarming manifestations of these cases attract the special attention of the observer that they are published much more frequently than the large numbers of cases with a less noticeable course.

Trousseau (219), among his numerous observations of Basedow's disease, has seen very few acute cases S West (686) reports among his 18 cases only one acute case, that of a 16 year old girl Cardiac palpitation and slight dispnoea had been present for three months Then came "quite suddenly", and without known cause, an enlarge-

weakness which increased so rapidly that she was confined to bed At the same time there was palpitation, loss of appetite, nausea, occasional vomiting, rapid emaciation and the Basedow's disease signs Repeated rises in temperature preceded delirium; mental confusion and weakness were so great that death was expected at the beginning of the third month of illness However, the patient improved again, and remarkably soon Then the disease signs including exophthalmia and goiter became worse again, bulbar signs appeared, then came delirium and an increase in the pulse rate to 188, with exceptionally forceful heart action and a temperature rise Death came three and a half months after onset of the illness Attacks of gallstone colic preceded the outbreak of Basedow's disease in the case of a 36 year old patient These began with abdominal distress, repeated vomiting, and a rapid loss of strength Death occurred after a two and a half month course of the disease One woman had a febrile illness which kept her in bed for six weeks She did not recover properly In the course of the Basedow's disease she became mentally dull and had hallucinations After four months the patient withdrew from treatment unimproved But she was so ill that imminent death could be predicted In the case of a 22 year old girl the disease began with headache, vomiting, and overfatigue from a long walk Death occurred two months and seven days after the beginning of the illness A mild *Angina tonsillaris* hastened it Fr Muller then described still another case, that of a 25 year old girl Following numerous fluctuations and considerable loss of weight, death occurred in the tenth month of the disease Later, the same observer (2718) mentioned the acute progressive course of a man who showed enlargement of the right ventricle with considerable unexplained hypertrophy of its wall

A woman of 33 observed by Arneill (1934) had rheumatism in nearly all of her joints A rapid enlargement of the thyroid gland came after the menses had ceased for five months After three more months this was followed by anxiety, excitement, palpitation, and general nervousness Vomiting and diarrhea were accompanied by loss of strength The patient lost 35 kg of weight within four months After four more months had passed the temperature exceeded 41°, the pulse rate exceeded 200 beats per minute Death followed

Atkinson (2254) reported the acute case of a man of 55 whose death came eleven or twelve weeks after the outbreak of the disease After he had lost a great deal of money a change in his personality was noticed He became easily fatigued and very irritable, his speech was rapid and hasty He suffered from palpitation and the signs of Basedow's disease were discovered, only the eye signs were absent His condition became rapidly worse Five weeks later diarrhea and vomiting and violent tremor began Soon afterward an outbreak of mania occurred A wide gap of the palpebral fissure appeared Death was preceded by a rise in temperature, extreme tachycardia and delirium

The acute character of Brewer's case (1944) became evident only several weeks after the first appearance of the symptoms A 43 year old man without hereditary predisposition, and previously healthy developed quite suddenly, and with severe pain, a massive enlargement on the left side of the throat Swallowing caused pain, and a conspicuous lassitude became evident After four or five days pain, difficulty in swallowing, and swelling all diminished On the other hand, the patient complained of lassitude and palpitation, he became easily excited, and began to be emaciated in spite of good appetite These signs progressed A few weeks later the neck enlarged again rapidly, but this time without pain and on both sides more on the right than on the left The eyes protruded There was also tremor, sweating, thirst, polyuria, and pigmentation of the skin Six months after the onset of the illness mental confusion

within five or six weeks after the onset of the disease in the cases of Pilet-Fout (1139) (see §154 above), G Rankin (1493) (see §129 above), Dana (2163), (see §129 above), Grube (1317) (see §232 above), Nonne (1628, in a 25 year old lady with no predisposition) Ratjen (1638) mentioned an acute case of Basedow's disease resulting from panic This illness ended fatally following diarrhea, vomiting and adynamia. Magnus Levy (1615) saw such a case involving a 20 year old woman, R. v. Hosslin (3140) reported the case of a young girl after rape, R. Spencer (1662) a 16 year old girl, Murray (2213) offers 2 such cases which developed in association with an influenza A 29 year old woman of frail build was observed by J A Matson (2542 and 2713) She had entered the hospital because of a slight inflammation of the throat There it was found that she had a moderate enlargement of the thyroid gland with pulsation and a *bruit*, an acceleration of the pulse to 140 and over, an accelerated respiratory rate, a tremor and lid signs On the eleventh day of illness vomiting began which lasted six days The patient became very restless, the temperature rose to 38 8°, and the pulse to 170 Death occurred on the eighteenth day after the onset of the throat inflammation In a case observed by A J Campbell (2157) the outbreak of the acute disease seemed to have been caused by internal administration of iodine. A servant girl who had previously been healthy had, a few days before, noticed a swelling of the throat Syrup of hydroiodic acid was prescribed, three teaspoonfuls daily About three weeks later very rapid pulse, heat sensations, increased sweating, palpitation, strong pulsation of the abdominal aorta, tremor of the whole body, and great excitability developed On the following day exophthalmia and v. Graefe's sign were discovered Four weeks after the appearance of the acute signs the skin became jaundiced and vomiting occurred Death occurred twelve days later, after progressive emaciation

A woman observed by W Gilman Thompson (2773) had taken 50 grams of thyroid extract She was brought into the hospital in a state of acute toxemia, and died soon after Béclère (2170) who, himself, had an opportunity to observe a severe case of acute thyroidism (see below) reported that in Paris hospitals 1 adult and 1 or, indeed, 2 children who had been undergoing thyroid gland treatment for therapeutic purposes died suddenly, as he believed, from cardiac arrest Turk (3199) recalled that he had seen a fatal case of acute thyroidism involving a previously healthy male

In a series of cases with an acute outbreak the illness lasted several months

A woman at the Ziemssen clinic, whose case history Freudenberger (430) reports, developed the symptom complex of Basedow's disease in a few hours following a night of continuous, wild dancing During the following week the disease became severe Other cases which followed a course lasting several months after an acute outbreak are mentioned: 1 by Windle (534), a woman of 35, 1 by Hale Hite (687), a woman of 21, 1 by Hardy (516), a woman of 45, 1 by Gwynne (897), a woman of 34, 1 by Ditisheim (1293), a man of 28, 1 by Diller (216a, see §135 above), a woman of 46, 1 by Hirschlaff (1733), a girl of 21, 1 by R T Williamson (1523), 2 by Rose Bradford (1538); 1 by Potts (2223), 1 by Harvey Sutcliff (1796), a woman of 33; and 1 by Murray (1891), a man of 30

Fr. Muller (1134) carefully described four such cases They included a 22 year old girl, a 36 year old woman and two 48 year old women None of these cases had a hereditary predisposition. In the case of a 48 year old woman the disease developed immediately after a violent shock From that moment on the woman felt a general

and muscular weakness, followed two days later by a considerable swelling of the thyroid gland and a new attack. *The pulse rate rose from 80 to 100, and the eyes* protruded rather distinctly. During the following days the signs increased, including perspiration, tremor and sleeplessness. This signified the climax of the disease. Five days later all the signs of the disease had disappeared. The neck circumference had returned to its former dimensions of 34 cm. This girl had developed a small goiter previously during an earlier attack of chlorosis. Holzknecht (3130) mentioned a case in which a Basedow's disease had developed in the case of a 33 year old woman after a delivery. In the course of three months she had developed a severe form of the disease. After one treatment by X-rays the signs disappeared almost completely, and *after two further X-ray treatments the woman recovered in the course of three* months.

In children an acute form of Basedow's disease has been observed a few times. In spite of rather turbulent symptoms at the beginning the outcome was favorable.

Labarraque (88) reports such a case from the observations of Trousseau (94). A 14½ year old healthy boy could stand sea bathing for a very short time only. During a stay at the seashore a swelling developed on the neck which became distinctly larger within a few days. From then on he could no longer endure sea bathing at all. When he tried to bathe he suffered an attack of choking. In spite of iodine treatment, the goiter grew larger and shortness of breath increased. After temporary improvement *the swelling began to grow rapidly. The boy was almost asphyxiated. In the* thyroid gland pulsations were readily visible. The eyes protruded from the sockets, and the pulse rate rose to 124. Bloodletting, emetics, laxatives, compresses on the neck, and digitalis, soon improved the situation. Three weeks later the boy was fully convalescent. The exophthalmia had disappeared, the pulse went down to 72, only a slight swelling of the thyroid gland remained.

Better known is Solbrig's (249) case of an 8 year old boy who became more and more restless and excited after receiving a prize which he had coveted. *He had palpitations*, definite prolongation of the heart sounds, pulse rate of 120, accelerated *respiratory rate, profuse sweating, and, two days later, a swelling of the thyroid* gland and exophthalmia. After two more days the progress of the disease was reversed. On the twelfth day following the onset of the illness the boy was completely restored to health.

A 10½ year old girl was observed by H. Muller (853). The disturbance began with an awkwardness in the use of the hands although there was no chorea. Two weeks later in rapid succession came goiter, exophthalmia, and palpitation. There was a noticeable *widening of the cardiac dullness, a pulsation of the chest wall could be observed* from a distance. The pulse rate was 120 beats per minute. There was a *bruit* over the goiter. After a month, during a mild case of diphtheria, all these signs disappeared completely.

Demme (964) observed a 5 year old son of healthy parents. Ten days after an outbreak of scarlet fever, and two days after the beginning of desquamation came an outbreak of exophthalmia, two days later came a walnut-sized, pulsating swelling *of the thyroid gland, after another three days came* palpitation, pulsation of the carotids, and tachycardia. The pulse was 120 and forceful. A definite improvement showed with bed rest, cold compresses on the neck and a milk diet; after 8 weeks. After a sojourn of two or three weeks in the country, the cure was complete.

A. Kocher (2197) reported an 8 year old boy who had a goiter for a long time

and hallucinations began. Death occurred five days later, with a temperature rise to 40°.

In the case of a 25 year old girl demonstrated by Rudinger (2329) it appeared, as in Campbell's case described above, that the acute Basedow's disease was induced by the administration of iodine Two months previously a rapidly increasing enlargement of the lower anterior part of the throat was noticed. After administration of an iodine salve, partial regression of this mass occurred Relative well-being was attained for about 3 weeks Then came general discomfort and, two days later, a complete alteration in the mental condition of the patient. This girl who had been calm became excited, ill-natured, anxious, and showed great motor unrest. The eyes protruded, the face took on a staring expression, and palpitation became disturbing At the same time uncontrollable vomiting began such that only a precarious feeding schedule by syringe was possible No report is available about the final outcome of the illness but death is not improbable

§253. There are still those cases to be considered in which the Basedow's disease developed rapidly to full intensity, and which, after a respite of a few days, weeks, or months, regressed again to complete recovery.

A recurring case of this sort, which ended in a complete cure after the third relapse, has already come to our attention among Konigstein's 3 cases (see §249) Fletcher (137) observed an acute outbreak and rapid recovery in two cases, as did G R Murray (2213) in the case of a 29 year old nurse. Strumpell (1918) stated that he had seen almost complete recovery of several acute and seemingly very severe cases R Stern (3060) reports such a case Here, attention is also called to Friedrich's case (191) as already reported, the case of a 30 year old servant girl Chvostek (332) described the acute onset of Basedow's disease in the case of a 23 year old lieutenant who had been under treatment for recurrent syphilis The onset came after excessive drinking The hangover did not pass off The eyes took on a staring expression A few days later palpitation occurred and the pulse increased to 120 beats per minute There was a feeling of depression associated with rapidly increasing emaciation and frequent vomiting Then the eyes protruded and the thyroid gland became enlarged. There were marked pulsations in the throat, and tremors in all the limbs, during any slight excitement Galvanic treatment resulted in considerable improvement Rampoldi (499 and 527) reports a young woman who developed the symptom complex of Basedow's disease during her wedding night Signs related to the heart and throat soon disappeared again When Quaglino saw the patient, there was only a moderate exophthalmia The case described by Nias (1063) described above (§119) should be recalled here Fourteen days after a severe epileptic attack, a staring expression of the eyes was noticed Then exophthalmia combined with lid signs developed more and more distinctly Within a few weeks all the signs disappeared again without the development of the full symptom complex W. Moore (561) relates that he saw the signs of Basedow's disease break out almost suddenly following a violent shock A young girl, after opening a letter telling of the death of her brother, was attacked by violent palpitation. The pulse rose to 140, the eyes protruded, and the thyroid gland swelled up After 48 hours the exophthalmia went away, the pulse sank to the normal rate, and the neck swelling became reduced In the case of a woman observed by Debove (1836), the complete symptom complex developed within a few days and, indeed, part of it already within a few hours following emotional upset After seven or eight months she was almost completely cured Only definite signs of hysteria remained A girl of 22 came under Noorden's treatment because of chlorosis (1624)

was dry Ecchymotic spots appeared on the body Rapid and significant improvement followed treatment with Rogers' serum Seven weeks after coming under treatment, the girl left the hospital free of all symptoms, three months later no disease symptoms at all were evident

A similar case of a 29 year old woman is reported by W Gilman Thompson (2773) It was said that she had developed unusually nervous excitability, restlessness and palpitation, following a heavy cold Two weeks later a symmetrical, pulsating goiter, pronounced tremor, and a firm swelling on the legs appeared There was a loud systolic murmur over the apex and base The pulse was weak and very rapid, up to 144 The patient perspired heavily, had a dry tongue, and vomited frequently There was pronounced leucocytosis The temperature rose to 40° After the use of Rogers' serum the condition soon improved Five months later the woman was a picture of good health

In some cases, pregnancy, uterine bleeding, or a gynecological operation precipitated an acute Basedow's disease ending with recuperation

Thus, H W Freund (520 and 543) saw in a *Gravida III*, in the seventh month of pregnancy, the development, in rapid succession, of the Basedow's disease signs, a small goiter had appeared already during the first pregnancy The birth intensified palpitation and thyroid enlargement But from the third day after this birth all signs disappeared rapidly, followed by a complete cure

A 21 year old woman observed by François (2068) had rapid pulse, thyroid enlargement and exophthalmus following a metrorrhagia The neck gradually attained a circumference of 36 5 cm Galvanization therapy was soon followed by decided improvement Only the rapid pulse remained C Hirst Barton (2456) observed, following a gynecological operation, the sudden occurrence of a tachycardia up to 160, protrusion of both bulbi, and swelling of the thyroid gland These signs soon disappeared The woman was said to have had such attacks since she had been a girl, but lately had been free from them

A 60 year old woman with a goiter had a gynecological operation by Himmelheber for correction of a uterine prolapse The goiter disappeared at that time, and symptoms of acute hyperthyroidism developed, including dilatation of the heart, rapid and irregular pulse, rise in temperature, and delirium These occurrences were interpreted by Himmelheber as related to the rapid reduction of the goiter It is problematical, but not out of question whether this could have been brought about by the use of iodine We do know that in predisposed individuals even very small doses of iodine can produce a rapid resorption of the goiter, thereby precipitating an outbreak of thyroidism

The case history of a girl of 17 has been contributed by H Moses (2864) The symptoms of Basedow's disease developed in rapid succession immediately following an operation for a branchial cyst Within eight weeks they had become mild, but retained all the essential characteristics Up to that time no trace of Basedow's disease had been present After a brief interval the abnormal changes seem to have disappeared spontaneously

Several times the flare-up of an acute, mild, temporary Basedow's disease has been set off by surgical treatment of a simple goiter

Eight days before the examination the goiter had grown rapidly and developed a *bruit* At the same time palpitation, tachycardia and exophthalmia became evident The thyroid enlargement was firm and elastic, with a definite *bruit* and a systolic thrill Further signs did not develop Those present regressed after rest in bed. Three weeks after the appearance of this large goiter it was hardly more than plum-size, rather hard, and with no vascular signs

A 13 year old girl, observed by Zuber (2036) had a swelling on the neck for several months but no illness Rapid emaciation, lassitude, palpitation, tremor, retraction of the upper lids, slight protrusion of the eyes, and repeated watery diarrhea occurred after the beginning of iodine treatment In spite of an intercurrent rheumatism of the joints with pericarditis and chorea, the Basedow's disease signs improved Six weeks after the appearance of the acute signs only a slight acceleration of the pulse and a small hard lump in the right thyroid lobe recalled the recent Basedow's disease

Similar to Kocher's case just described was a sudden swelling of a previously harmless goiter which had been present for 25 years in the case of a man of 55 observed by Gauthier (1104) This man lived in a goiter region During one night the enlargement, which affected chiefly the left lobe of the thyroid gland, reached so great a size that tracheotomy was contemplated However, application of leeches caused the difficulty soon to yield During the following days predominantly one sided signs of Basedow's disease developed, including tachycardia, tremor, exophthalmia, and sweating, the last two signs being chiefly on the left side After two months all of the signs gradually disappeared

A young woman reported by Michalski (2716) became suddenly ill without definite cause, she suffered from palpitation, dizziness, constipation, tremor, and excitability Also, the eyes seemed to have grown larger Michalski discovered the full picture of Basedow's disease He, himself, had the opportunity to confirm that, in somewhat less than a week,
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be discovered of t

In a few cases of Basedow's disease with acute outbreak and without definite cause, a rapid turn for the better and eventual cure followed treatment with serum. According to our other experiences with the effects of various sera, however, it seems to me questionable whether the unexpectedly favorable outcome was due to their use

A 20 year old man with no predisposition was observed by Thiengen (2587) He suddenly fell ill without known cause The symptoms included palpitation, shortness of breath, and pains in the chest In a few days the dyspnea reached an alarming degree There was a shallow pulse of over 140 beats per minute, exophthalmia, tremor and a temperature rise to 39 7° After the administration of antithyroid serum, so great an improvement was shown that the man could be discharged from treatment about ten weeks after the beginning of the illness A similar case is mentioned by Peters (256), that of a 45 year old woman A 29 year old girl under treatment by Rogers (2736a) had complained, two weeks before the outbreak of the acute illness, of nervousness and sleeplessness She then developed extreme weakness, tremor, nausea, diarrhea, a temperature rise, very violent heart action, strong carotid pulsation, very rapid pulse, and accelerated breathing The thyroid enlargement was only slight and was of soft consistency. Exophthalmia was absent. Five days later the temperature rose to 40°, the pulse rate to 136, and the respiration to 36 The tongue

was dry Ecchymotic spots appeared on the body Rapid and significant improvement followed treatment with Rogers' serum Seven weeks after coming under treatment, the girl left the hospital free of all symptoms, three months later no disease symptoms at all were evident

A similar case of a 29 year old woman is reported by W Gilman Thompson (2773) It was said that she had developed unusually nervous excitability, restlessness and palpitation, following a heavy cold Two weeks later a symmetrical, pulsating goiter, pronounced tremor, and a firm swelling on the legs appeared There was a loud systolic murmur over the apex and base The pulse was weak and very rapid, up to 144 The patient perspired heavily, had a dry tongue, and vomited frequently There was pronounced leucocytosis The temperature rose to 40° After the use of Rogers' serum the condition soon improved Five months later the woman was a picture of good health

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The earliest observation of this sort is contributed by Rösen (27). A seton had been drawn through a goiter cyst, and a cloudy, greenish-brown oily fluid was discharged. Eight days later the 21 year old patient had palpitation, lassitude, and rapid emaciation. It was expressly stated that no traumatic fever was present, and that a small amount of normal pus was discharged Rösen, evidently a very good observer, added that he had never seen such a manifestation, especially such a rapid emaciation accompanied by good appetite and good digestion, even with the largest abscesses. He considered the cause to be "a poisoning due to resorption of goiter substance"

A Kocher (2107) reported a 24 year old woman in whose family goiter was common, and whose brother had Basedow's disease After the first delivery the goiter, which had been present for three years, began to grow. But it caused no discomfort A puncture of the easily palpable colloid struma, was immediately followed by tachycardia of up to 120 beats per minute, tremor of the hands, profuse perspiration, and bilateral exophthalmia After a few days these signs gradually disappeared again. The goiter remained uneffected A few weeks later a goiter operation on both sides effected a permanent cure A 30 year old man with no hereditary predisposition developed signs on the very day that an excision of a simple rightsided goiter was carried out These included excitement, tremor, tachycardia to 140, retraction of the upper eyelids, slight exophthalmia, and perspiration There was no rise in temperature The wound was in perfect condition All the signs disappeared after a few days, and the patient remained healthy thereafter A similar observation was made by Thevenot (2124). A young woman developed rapidly progressive manifestations of *Basedowism* after intraglandular enucleation of a goiter cyst. After tampons were used instead of drainage, the alarming signs disappeared

Other kinds of manipulation involving uncomplicated goiter may also produce an acute outbreak of Basedow's disease.

This is shown by Brieger's case (2623) A man of 40 had a slowly developing goiter since his youth A quack had been treating the goiter with vibration massage daily for about a month Thereupon, suddenly, palpitation set in and, in unequivocal form all the signs we see in Basedow's disease After discontinuance of this treatment and the introduction of hydropathic treatment the exaggerated heart action and the other Basedow's disease signs gradually disappeared The man had never had any similar illness before

Several noteworthy observations have been made recently on the development of Basedow's disease signs following X-ray treatment of a simple goiter.

A conspicuous case of this sort has been recounted by Kienbock During the days immediately following the X-ray treatment the goiter became smaller After the fourth day came general debility, tremor in the legs, palpitation, a rapid pulse of up to 140 per minute, and loss of appetite v Graefe's sign was also present Both lobes of the goiter and the isthmus were exposed to a rather powerful dose of X-rays It is quite conceivable that the irradiation, while acting destructively upon the more superficial parts of the gland parenchyma, permitted a more abundant supply of blood, a growth of gland cells, and an increase of the gland function in the form characteristic of Basedow's disease

F. Chvostek (3219) has seen a similar case A woman had X-ray treatment of an

old goiter in a manner which, according to present-day ideas, was much too energetic. Conspicuous Basedow's disease resulted. Chvostek suggested that perhaps more profound disturbances and a reactive inflammation had been produced. This, then, by analogy with the observations of Basedow's disease following acute, non-suppurating thyroiditis, (see below under Etiology) led to these manifestations.

In a case of a 31 year old woman, contributed by H. A. Schmidt (3185), a rather acute Basedow's disease occurred 12 years after X-ray treatment. This patient's benign goiter had decreased considerably two years after the discontinuance of the X-ray treatment. Then the circumference of the neck again increased by 2 or 3 cm. A repetition of the X-ray treatment was refused. About a month after the occurrence of the acute symptoms, death from a heart attack occurred suddenly. In this case the X-ray treatment probably is not responsible for the occurrence of the Basedow symptoms.

Use of thyroid-gland preparations, as we have already seen (see §252 above), can often produce acute thyroidism. Sometimes this takes on the pattern of a well-defined Basedow's disease. It should be remembered here that a mild, slight, or subsiding Basedow's disease can be acutely aggravated to a severe form by thyroid preparations (see §248 above).

As a rule the signs disappear entirely soon after discontinuance of the medication.

The first obvious case of this sort is described by Béclère (1172). A 31 year old woman suffering from myxedema took, by mistake, 8 sheep thyroid lobes at one time, or about 12 grams. In spite of this, everything seemed to go well. The treatment was continued with large doses, in the course of eleven days 92 grams had been taken orally. The signs of the myxedema improved visibly. But now a series of other signs appeared which form the characteristic pattern of Basedow's disease, tachycardia, accelerated respiration, occasional tremor of the hands, temperature rise, hot flushes, dermographism, outbreaks of perspiration, retraction of the upper lids[1], a high degree of excitement, sleeplessness, glycosuria (see §233 above) albumenuria, and polyuria. After a violent emotional shock there was also a rightsided hemiplegia with hemianesthesia and aphasia, signs which lasted only a few hours and were considered by Béclère the manifestations of a complex hysteria. Compare also the earlier case of a 10 year old boy (§221), contributed by Baldwin, and cases by Morrow, Ewald, and Ulrich, in which, after moderate doses of thyroid substance, signs of myxedema gradually disappeared and Basedow's disease signs developed.

Another case of acute thyroidism which bore all the features of a completely developed Basedow's disease was described by Notthaft (1746). A 43 year old man under doctor's orders took almost 1000 English thyroid tablets within a period of five weeks for the purpose of losing weight. He succeeded in losing nearly 15 kg but the following signs were discovered at the beginning of the sixth week of this "cure": tachycardia to 120, visible carotid pulsation, exaggerated cardiac apex beat, accelerated respiration, dry cough, a not inconsiderable enlargement of the circumference of the neck to 47 cm, moderate tremor strongest in the hands and tongue, increased gape of the palpebral fissure, v. Graefe's sign, definite exophthalmia, slight reddening of the face, greatly increased perspiration, glycosuria (1% sugar, see §233 above) and

[1] "De l' éclat du regard se rapprochant de l'exophthalmie"

polyuria. Although the appearance of the patient was not bad, he had a feeling of depression and dissatisfaction with life, was much excited, and slept poorly. The signs disappeared soon after discontinuation of the medication. After two weeks the urine was free from sugar and six months later all the signs had disappeared entirely

A 24 year old pharmacist, observed by Bomet (1820), ingested one sheep-thyroid gland a day as treatment for a *dermatitis exfoliativa*, then, against the doctor's orders, he took 6 to 9 thyroid glands daily for eight days Great motor and mental unrest and a psychosis developed rapidly (see §160 above) At the same time palpitation, tachycardia, thyroid enlargement and tremor set in After discontinuation of the medication there was an improvement, but all the symptoms returned following renewed use of 6 to 8 thyroid tablets daily Permanent discontinuance of the medication resulted in a complete cure

In 3 more cases, an uncomplicated goiter had been present for some time Thyroid tablets were taken for the purpose of reducing the goiter. A 14 year old girl had a slight "blown-up neck" since her fourth year; this was gradually increasing in size Upon the advice of a doctor six months previously she came under Stegmann's (2764) observation She had used 1½ thyroid tablets daily Then she had to interrupt the treatment because of excessive palpitation The condition improved for only a short time Soon an unusually disturbing palpitation returned together with a profuse diarrhea, sweating, shortness of breath, and tremor of the entire body. A moderate exophthalmos was discovered, wide gape of the palpebral fissure and v Graefe's sign were evident Repeated X-ray treatment of the goiter, of about twelve minutes each, resulted in a complete cure after four months

A 21 year old farm worker reported by A Kocher (2197) took 2 grains of thyrein (Bayer) daily for ten days and then one grain daily for ten more days because of a goiter which he had for six years Subsequently he developed headache, dizziness, tremor of hands and legs, sleeplessness, sensations of heat, extreme thirst, rapid pulse, occasional diarrhea, and vomiting He lost much weight and became weak v Graefe's sign was evident The goiter did not decrease in size but softened gradually Kocher had no doubt that exophthalmos would have developed But all symptoms disappeared from the moment of discontinuance of the medicament Two weeks later no more signs of Basedow's disease could be found, except a slight tremor The goiter was harder and somewhat smaller

Elliot described as "artificial thyroid toxemia" the case of a 22 year old man who had had a harmless goiter since childhood Several weeks before the medical examination he noticed a sense of swelling and constriction in the throat, he perspired profusely and became restless and excited There was a pulse rate of up to 126 per minute, a carotid pulsation, and a slight tremor of hands, tongue, and the closed eyelids The tendon reflexes were active, exophthalmos was absent It was learned that he had started to take thyroid extract 4 weeks before the consultation Since he noticed no effect upon the goiter, he had gradually increased the dosage During the last week he had taken 200 tablets of 0 3 gram, a total, therefore, of 60 grams It is striking that during all this time he had not become thinner, but that he had gained weight. All manifestations of illness finally disappeared with the discontinuance of the tablets

Johnston (1120) repeatedly made the observation upon himself that, when he took 2 or 3 tablets 2 or 3 times daily for two days in succession, his pulse rate increased from 70 to 120 and above He also noticed palpitation, redness of the face, a sensation of heat, profuse sweating even in cold water, a slight temperature elevation and a fine tremor

Byron Bramwell's (1823) observation also is of interest He treated a 34 year old woman suffering from Basedow's disease with 2 thyroid tablets a day During the treatment this woman, who tolerated the medication very well, was feeding her previously healthy 6 months old child at the breast A week after the beginning of the treatment the child had an attack of profuse sweating, restlessness, sleeplessness, and vomiting The symptoms disappeared at once when treatment was omitted by the mother It returned when she took tablets again This was repeated several times

In the occurrence of an acute thyroidism following administration of thyroid-gland substance individual disposition plays a very important part

v Bruns (1411b) has used thyroid preparations on 350 goiter patients and has never seen any disturbing symptoms V Angerer (1398) treated 78 goiter patients with thyroid extract, usually for weeks at a time, and only occasionally observed mild signs of thyroidism These disappeared following discontinuance of the medication Only in the case of a 50 year old neurasthenic the pulse rate rose to 140, there was tremor over the entire body, sleeplessness and nervous excitement appeared There was no evident influence on the goiter Zum Busch (1525), in his extensive experiments with the thyroid tablets of Burroughs, Wellcome & Co of 0 33 gram, made the discovery that they had only a mild effect on healthy persons Among 68 cases in which he used the medication for therapeutic purposes he had seen signs of thyroidism only 4 times Among these cases was a girl whose Basedow's disease had changed to myxedema (see §221 above) Among these 4 cases the signs were only minimal and disappeared following a reduction of dosage An observation reported by *Becker (1271) was made on a 2½ year old child which had once taken 90 thyroid* tablets of 0 3 gram each without suffering any harm (§233) I would like to point here to the fact emphasized above (§223) that the basal metabolism of healthy persons and that of goiter patients is, as a rule, only slightly increased by the administration of thyroid preparations But the basal metabolism of myxedema patients on the contrary, is very much influenced and their nitrogen turnover raised considerably

In rare cases of individual predisposition, a condition analogous to acute thyroidism, is produced by the administration of iodine compounds This has been called acute iodinism A very severe case of this kind has already been mentioned above (see §248, R Breuer's case) also the cases of Campbell and of Rudinger (§252) and Zuber's case (§253) An acute, but less severe, course is also described in several other cases

Thus Chvostek (332) observed that in the case of a lieutenant who was being treated with potassium iodide for syphilis, a small goiter which he had had for a long time began to grow rapidly, at the same time he experienced profuse sweating, palpitation, tremor of hands and feet after the slightest excitement, a high degree of mental unrest, and, finally, protrusion of the eyes There was no hereditary predisposition Discontinuance of the iodine treatment soon resulted in improvement

In 4 among 80 cases reported by A Kocher (2197) internal and external use of iodine preparations influenced unmistakably the development of Basedow's disease One case was a so called acute iodinism A 40 year old woman who had had an uncomplicated goiter for many years took iodine both internally and externally for a short time, with no apparent effect on the goiter On the other hand she developed palpitation, rapid pulse, tremor, profuse perspiration, frequent watery diarrhea,

great excitement and, finally, marked protrusion of both eyes. After discontinuance of iodine medication the condition remained stationary for a time. Gradually it disappeared entirely and the patient remained cured.

An additional case which belongs here is reported by Warschauer (2893) A previously healthy 28 year old woman had been taking an inunction treatment for a mild skin disorder After taking 72 gram of potassium iodide internally for four weeks she complained of lassitude, other effects included rapid emaciation, acceleration of the pulse to 120, loss of appetite, frequent diarrhea (up to 20 times within 24 hours), erythema extending over the entire body, and swelling of the face, especially the eyelids She was given 0 3 gm thyroid daily Thereupon the cardiac disorder increased to such an extent that they had to be omitted Emaciation increased again In seven weeks the patient had lost 30 kg, and could no longer leave her bed She developed violent tremor and became completely sleepless The pulse was uncountable, and at times she became delirious The face became still more swollen and the hair began to fall out For a time a distinct swelling of the thyroid gland was evident One more attempt was made to administer thyroid tablets, at first ½ a tablet a day for three days, then 3 tablets daily From then on, an improvement began which made rapid progress with administration of sodium phosphate. Long continued observation showed no relapse

Holzknecht (3139) had seen 2 cases in which the Basedow's disease symptoms developed acutely following iodine treatment of a simple goiter. A 31 year old woman's goiter had not been present very long Its size fluctuated The Basedow's disease which appeared after a brief treatment with iodine reached an advanced stage within three months Several X-ray treatments resulted in considerable improvement In the second case, that of a 39 year old woman, a goiter had been present ever since youth After iodine treatment continuing for one year Basedow's disease signs developed acutely Only the exophthalmos was absent After 20 X-ray treatments within ten months, the signs, with the exception of the goiter, disappeared almost entirely.

Cereoli (3098) reported two cases in which the use of iodide of potassium caused symptoms of thyroidism A 51 year old woman, burdened by a large goiter, took, by mistake, 15 gram of iodide of potassium at one time, before breakfast The goiter grew smaller, but the woman lost weight and developed the signs of Basedow's disease The goiter again became enlarged After a few months the woman was fully well again A 54 year old woman had, besides goiter, arthritis and a cardiac disorder She was asthmatic and very obese After an experimental trial of potassium iodide the patient lost weight rapidly, the cardiac defect became worse, and tremor appeared No change was evident in the goiter. After discontinuance of the iodine treatment the signs of thyroidism disappeared within several months

Rendle Short (3191) observed the outbreak of a typical Basedow's disease in a case in which iodoform was applied externally to a wound The symptoms lasted for a year

In the great majority of cases the course of iodothyroidism is less rapid. We shall concern ourselves with this interesting condition more thoroughly later on.

The Duration of Basedow's Disease

§254. The duration of Basedow's disease in chronic cases is extremely variable It may extend over a period of years, with numerous, often con-

siderable fluctuations, as mentioned above (§247). The majority of the cases do not remain under observation long enough to permit a definite statement about their duration and final outcome. But in a few cases we know that the disease has lasted for over 20 years

During this time, not infrequently, there are shorter or longer periods of remission, with relative well-being or, in fact, real intermissions of rather long duration which can be misinterpreted as a cure (see §249 above, p. 560, concerning relapses)

H Mackenzie (918) stated that he had seen a case of 20 years' duration Boinet and Bourdillon (950) mentioned a case in which the disease lasted 21 years Of 14 Basedow's disease patients from the almshouse in Berlin, as reported by Grohmann (1202), the disease had been present for 19 years in 2, for 18 years in 1, and for 8 years in 1 *Among Pässler's 51 cases of Basedow's disease in polyclinic was a 46 year old* woman who stated most definitely that goiter, exophthalmia, and a series of nervous difficulties had appeared while she was still in school and that they had remained ever since in varying degree Three patients had suffered from Basedow's disease for from 4 to 8 years, 4 patients for from 2 to 4 years, 4 for from 1 to 2 years In the rest, the disease had occurred within the course of a year, or only a few weeks Among the numerous Basedow's disease cases which Přibram (2727) observed for a long time was 1 of more than 20 years duration, which ended in complete recovery Among the cases of typical Basedow's disease collected by R Stern from the First Medical Clinic in Vienna, 1 was of 16 years duration, 2 regained their health after 11 years One patient died after 14 years of the disease, and 2 after 11 years Among the cases designated by him as Basedow's disease was one believed to be of 50 years duration, 3 of 35 years, 2 of 30 years, 6 of 25 years, 5 of 15 years, and 8 of 10 years duration Chvostek (3219) knew cases of patients who suffered for many years from severe Basedow's disease symptoms and yet lived to an old age Among 80 cases which W Gilman Thompson (2773) had collected from his cataolgue, the duration of the disease ranged between 25 years and 6 weeks In more than a quarter of his cases it was from 2 to 4 years According to W Moore's (561) experience the disease is, as a rule, more prolonged in women than in men In the 3 cases which he had seen among males the illness lasted not quite 1½ years

In childhood Basedow's disease often pursues a more rapid course (see §295 below)

§255. It would be of great practical importance, as well in the interest of prognosis as related to our therapeutic procedures, to have a reliable knowledge of the outlook for a cure on the one hand and of the danger of a fatal outcome *on the other during the spontaneous course of Basedow's* disease. Hardly a single case has come to our attention which a physician had not treated We permit ourselves no illusions as to the uncertainty of medical therapy as an influence on the course of Basedow's disease.

Even though we know that the most extensive dietetic regulation can, at best, only come to the aid of nature, still we can gain useful basic facts from a sufficiently prolonged observation of cases in which no surgical interference has been undertaken.

The Outcome of Basedow's Disease

§256. We have thoroughly elucidated the peculiarities of a group of cases of Basedow's disease with an acute course and those with a sudden transition to an acute phase (§251, §253, §248). We have seen that, in these forms, the danger of a fatal outcome is great. The more a case approaches this type in its occurrence and course, the more dangerous the outlook. For the disease may suddenly take a turn for the worse even though the signs do not seem very serious at first. One will, therefore, do well to be cautious in making a prediction. H Mackenzie (2537) estimates the mortality of acute cases at 30%. This estimate seems to me to be too low rather than too high If, on the other hand, complete involution of the symptoms does follow after an acute course (see §253 above), and a certain period of time has elapsed, one can count on a permanent cure much more certainly than in chronic cases in which single symptoms remain for some time. Possibility of a relapse, sometimes in a most severe form, may still be anticipated even after long intermission (see §249 above)

§257. Danger of death from the Basedow's disease itself is less in the case which begins with an insidious onset and pursues a chronic course Death is caused most frequently by myocardial failure following prolonged cardiac over-activity and dilatation of the ventricle, by asystole, by exhaustion and extreme emaciation, by continual diarrhea, by uncontrollable vomiting, and, more rarely, by icterus (see §232 above) or by a severe mental disturbance (see §153 above). One must not overlook the lessened power of resistance of the patient who has had Basedow's disease for a long period of time He is more susceptible to consumptive or intercurrent acute diseases In not a few cases tuberculosis of the lungs, pleuritis, pericarditis, a previously existing valvular disease of the heart, or one arising in the course of the disease, with its resulting conditions, or a brain hemorrhage, etc , constitute the cause of death It is one of the well known facts of surgery that goiter operations endanger Basedow's disease patients more than other goiter sufferers.

Statements in pertinent literature concerning the mortality rate of Basedow's disease differ, often, very widely, These variations result chiefly from the differences in the material upon which they are based The numbers of the many single reports are altogether too small to permit a generalization The hospital statistics of Basedow's disease cases, extending over a period of years, are onesided inasmuch as predominantly the more severe cases are sent to hospitals. The large numbers of patients with mild and incomplete forms either go to a doctor for a brief period and remain ambulatory, or, perhaps, are not correctly recognized and sail under a false flag. A fur-

ther source of error lies in the fact that only a few observers have taken the trouble to follow up the ultimate fate of improved or cured patients The mortality figure will be unusually high among a moderate number of cases, if several with an acute course happen to be included We cannot accept the proposed procedure of Buschan (1181, p. 22), and of several others before him, who estimate the mortality rate for Basedow's disease by comparing the known number of deaths and the total number of all cases published, although we are today in a position to work with much larger numbers For the total number of the cases, those from which the calculation has been made is only a fraction This fraction is not sufficiently well-known to us, and in many of the published cases we fail to find statements concerning subsequent course and outcome of the disease. Particularly the severe cases ending fatally show interesting variations of their symptom complex or course and consequently are considered worthy of publication. The far greater number of cases which do not differ in any way from the usual type, and the multitude of incomplete cases which certainly were often overlooked, during the first two thirds of the past century escape our knowledge.

Charcot (55) from among 40 collected cases, recorded 10 with a fatal outcome (25%). v Graefe (63, p 297) reckoned, on the basis of collecting all useful observations, 12% with fatal ending According to Dusch's (207) statement, there were 12 5% Gaill's (514) collection of cases show 10 out of 47 ending in death Bellingham (80) reported 4 lethal cases among 22 (18 2%) W B Cheadle (424) reported in 1879 on the

cation because of a closure of the glottis That corresponds to a mortality of 9 67% Among 18 Basedow cases which S West (686) reviewed, 3 died (7 9%) A 16 year old girl died after a short illness of an incompletely understood pneumonia The autopsy showed a persisting thymus A woman of 43 succumbed suddenly after a temporary improvement, and another woman of 43 died after a four year course of the disease There was a final rise in temperature to 43° Autopsy findings were negative No reports are available on the ultimate fate of most of the other cases

Among 12 cases treated by Hale White (687) in recent years whose subsequent condition he had inquired about, 7 had died after leaving the hospital In 5 cases cause of death was a concurrent disease (pulmonary tuberculosis, cardiac valvular failure, sepsis), 2 patients died suddenly The cause of death was not revealed by the autopsy In 1 of these cases it was acute Basedow's disease (see §252 above) The other, a woman of 20, collapsed from an electric current she had applied to herself after seeing it used for other patients The disease had lasted for somewhat over a year Since we can indeed only count the first of these two deaths as caused by Basedow's disease, the re-

and in the other cases after 6 years or more If we take these 5 cases into account, we obtain a mortality rate of 12 5% In 1902 H Mackenzie mentioned (2205) six fatal

cases among 52 patients (11 5%) and in 1905 he estimated (2537) that 25% of Basedow's disease cases die of this disease sooner or later. From the admirable statistical study made by R T Williamson (1523) on 45 Basedow cases observed in the Manchester Royal Infirmary during the years from 1884 to 1896 and on 5 ambulatory cases we learn that 4 died during the stay in the hospital and 2 later. That gives a mortality rate of 12% All of those who died in the hospital had the disease in a severe form, in one case it was acute (see §252 above). In only 24 cases the observations extended over more than 4 years and it may well be that 1 or 2 more of these cases ended fatally. According to statistics assembled from St Thomas' Hospital, which Williamson used for comparison, 4 among 50 cases of Basedow's disease reviewed between 1870 and 1894 ended fatally while under treatment (8%) The conditions are therefore quite analogous Clarke (1546) had the opportunity to obtain information concerning 42 patients with Basedow's disease whom he had observed for 4 years, 5 had died as a result of the Basedow's disease and 3 from concurrent diseases If we consider only the first 5, the mortality figure is 11 9% Dock (2641) counted 2 fatal cases among 32 patients In one of these fatal cases the disease took an acute form, and in the other death was caused by another disease The cases do not seem to have been followed up any further

Eight among W Gilman Thompson's (2773) 80 cases died, making 10%; 1 or 2 other cases may have succumbed to the disease later Among the deaths recorded was one *following an acute course of 5 months duration In the other cases the disease* had lasted from 1 to 10 years Among 50 cases observed by A Rufus Baker over an average of 9 years, 6 were fatal, but none of the deaths was due directly to Basedow's disease or its complications, 2 patients died of pneumonia after 11 or 12 years respectively, 1 of childbed fever 12 years after the onset of the disease, and 3 died under the surgeon's knife Buschan's (1181) collection of about 105 published fatal cases was drawn from a total number of about 900 cases of disease The reckoned mortality rate was 11 6%, but he himself admits that this figure may exceed the actual conditions somewhat

Eulenburg (1567) reported that only 1 of about 400 cases of Basedow's disease under his care ended fatally, and that in this one case a goiter operation was performed against his advice Saenger (1646) stated that no deaths had occurred among 70 Basedow's disease cases Whether these two observers were in a position to learn about the further fate of their patients can be deduced from the statements given Nonne (1628) had 1 fatal case to report among 16 patients Among 89 Basedow patients treated within 10 years in the Leipsic Medical Clinic, Roper assembled (1911) case histories of 11 who died during their stay in the hospital A follow-up report of the subsequent condition of those discharged unfortunately is not given In 6 of the lethal cases, a sudden transition to the acute stage after a gradual development of the disease or after a chronic course of several years occurred After a few days, weeks, or months, the acute phase ended in death (see §248 and §249 above) Of the 5 entirely chronic cases, the cause of death in 2 cases was extensive pulmonary tuberculosis, and in 1 case contracted kidneys with acute uremia. The autopsy of 1 patient who died with acute symptoms disclosed a fresh pericarditis and endocarditis which must have hastened death If we take into account 7 fatal cases caused by the Basedow's disease itself, the result is a mortality percentage of 7 8%. This is probably somewhat too low because of the failure to take into account the fate of those who were discharged as improved or cured Syllaba (3065) was able to follow up for some time the progress of the disease in 50 out of 56 cases of Basedow's disease at the Medical Clinic in Prague Thirteen of these 50 patients died Three died from heart failure, 5 from cardiac asystole, and 1 each from cachexia, diarrhea following a feverish condition of

several months duration, an attack of mental derangement, and chronic nephritis with erysipelas. Three other cases showed advanced arteriosclerosis One had a chronic kidney inflammation, 1 had *typhus abdominalis*, in 1 case death from progressive paralysis followed the disappearance of the Basedow's disease symptoms On this basis, Syllaba reckoned that 18% of the fatalities were caused by the Basedow's disease itself. It seems to me that this figure does not correspond to the statements Basedow's disease should probably be held responsible for the fatal outcome of 12 cases That would be 24% This high figure may perhaps be explained by the fact that only the more severe cases were taken in R Stern (3060), by following up the further fate of his cases with typical Basedow's disease obtained statistically valuable results in almost 60 cases Among these, 16 died, but some other cause of death can be excluded with any certainty only in 10 cases Among those designated by Stern as *Basedowoid*, 9 of 75 statistically acceptable cases died If we combine the two groups in order to compare the values with other statistics, 11 among 125 cases can be attributed to the disease, a mortality rate of 8 15% Chvostek (3219) has gained the impression from the cases which he has observed, and whose course he knows, that Basedow's disease ends in death only seldom In a majority of cases it is a relatively innocuous disease

Anyone having had opportunities to perform many autopsies will admit that Basedow's disease represents only a tiny fraction among the causes of death Pearson makes a more exact statement in this respect Among 4100 autopsies which he performed within 10 years in St George's Hospital he found only 2 cases of Basedow's disease One of these, that of a 20 year old girl, revealed an acute joint rheumatism with cardiac valvular failure as the probable cause of death

In consideration of the sources of error mentioned above, which apply more or less to all the statistics given, we probably approach the truth rather closely as far as the mortality from the disease itself is concerned by an estimate of 8 to 12 cases out of 100 The average reckoned from the most acceptable collections gives us 11%. We must always bear in mind that, in general, the danger of death increases in proportion to the severity and the acuteness of the case

§253. In the majority of the cases of Basedow's disease the prognosis *quoad vitam* cannot be called adverse, nevertheless, *quoad sanationem completam* it is not very reassuring Certainly, in most cases with a chronic course a certain tendency to improvement sooner or later cannot be denied. But exacerbations and relapses are not excluded hereby Complete and lasting cures are rare, especially if the disease has already lasted for a long time and the signs are well developed and numerous Single signs, especially a certain degree of exophthalmia, often remain for a long time or permanently.

In fresh cases with obscure or incomplete disease signs, especially as long as the general condition has not greatly deteriorated, the outlook for cure or extensive improvement is relatively favorable, especially when the environmental circumstances of the patients permit suitable living conditions

Ballet (803) who could depend upon his wealth of experience, declared that a cure is the rule in mild and undeveloped cases (dans les formes frustes ou atténuées) while rare in well-developed cases. Most observers with wide experience express themselves similarly. That opinions still vary can be explained partly by the variety of observation material. It must also be considered in regard to the older statistics, that, since the diagnosis is no longer dependent on the old *trio* and we have learned to recognize the disease more easily in its early stages, prospects for healing are much more favorable in general. Naturally, much depends upon how strictly the various observers interpret the idea of a cure That a certain subjectivity reigns in regard to it is shown by various examples from pertinent literature. For practical purposes one may consider cured those patients who are able to follow their usual occupations and, with moderation, enjoy the pleasures of life free from subjective ailments. It may perhaps be recommended that, following Eulenburg's (2903) example, a distinction be made between absolute and relative cures The former are rather rare according to the experience of this author with nearly 800 cases. The latter he estimates at 25 or 30% at least

A. v Graefe (§63) was aware of the source of errors arising in statistical calculations because of interruptions in most of the observations He estimated the number of cases in which a complete cure was observed at 20%, and of those in which the possibility of a relapse was not excluded at 30% From this number another 38% remained in which all information concerning their further course was lacking v Dusch (207) reckoned the number of completely cured cases at 25% and those which were considerably improved at 46% Seven remained unchanged H Muller (782) mentioned 4 permanent cures among 18 cases or 22%

Přibram (1368 and 2727) was in the favorable position to observe the same patients for many years in one place and, partly, under controlled living conditions which made possible suitable care He has declared, as a result of his wealth of experience, that the mild cases in which the symptom complex was fully developed never ended otherwise than in recovery Such recovery usually came after the relatively short period of a few months or one to two years "always provided that one can hold them in a firm hand and completely control the living habits of the patient." He also saw very severe cases cured under the same regime, after a longer time. Sometimes only cardiac difficulties remained He had charge of a great number of very serious cases, in which Basedow's disease in spite of most threatening manifestations, reached a favorable conclusion and the cure remained permanent. In one very severe case, after several months of conspicuous improvement, a relapse occurred (see §249 above). Přibram is convinced that in Basedow's disease "we can count preponderantly on recovery".

Oppenheim (2417 and 3012) also had an extensive experience. He ex-

pressed himself similarly about the result of recent and mild cases. But if the disease has already been present for years and if it is far advanced, especially if definite marasmus, weakness, and enlargement of the heart exists, and the mental change is pronounced, the outlook for a cure is very adverse. Oppenheim could also point out cases which, even with extremely threatening symptoms, showed an improvement of long duration, bordering on a cure. Improvements are, in his experience, more frequent than cures. Klemperer (1986) also considered a complete cure of Basedow's disease quite possible, at least in mild cases. He cited the cases of 5 patients whom he had under observation for a long time The cure took place after one to one and one-half year's treatment Ewald (1960) stated that he saw quite a number of cases cured. Lenhartz (1604) and Saenger (1646) likewise found that the outlook for cure and essential improvement was, on the whole, not bad

Fr Kraus (1870) gathered, from his experience with the outcome of Basedow's disease, *that a relative cure is the most frequent outcome of the disease* Sometimes, there is even a *complete* cure Certain disorders usually remain in the so-called cured patients

F Chvostek (3219) expressed the conviction that the majority of the cases which could not be cured completely could still be greatly improved The ability to resume work was restored by giving the patients favorable living conditions, by suitable electrotherapeutic measures, and by water cures Weeks, months, even years may pass before such an end can be achieved He admits, however, that there are cases which cannot be influenced Chvostek also knew of cases in which the cardiac condition was so poor and such severe attacks of weakness and prostration occurred that death was to be expected hourly Yet, in spite the disease lasting for years, a cure was achieved

Strumpell (1918) and Eichorst (2820c) stated that, according to their experience, a complete cure was relatively rare

Kroug (2700) gained the conviction from 106 Basedow cases, of which only about 10 were severe, that an absolute cure is an unusual outcome of the disease Considerable improvement is the most frequent outcome Not infrequently he has observed remission and intermission of several years, or of as much as five years Two of his cases have remained free from relapses after 9 and 11 years respectively The sooner the patient receives treatment the better the chance for a cure.

Rehn (1901) said in his report at the Munich Naturalists Convention: "spontaneous cures certainly occur, sometimes, even, within a short time, but that is quite unusual"

Among 17 cases from Kocher's (2197) extensive observations, where no surgical treatment was employed, there was not one in which a complete and lasting cure was reached except in five acute cases.

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unfavorable from the beginning, the cure, under a rational therapy, was only a question of time. According to Bein-Barde (296) also, the outcome is usually favorable We have already considered Ballet's views

Among English observers with wide experience Hutchinson (664) says "Grave's disease is the most definite and striking example which we can find of a severe and protracted malady which, despite its severity and persistence, still has a natural tendency to recovery If the patient can survive for a certain time apparently the recovery is a matter of course We have no cases which are indefinitely progressive" In the case of a 46 year old woman with such severe symptoms that death was expected, the disease changed for the better after about 1 year, and 1½ years later the woman was cured except for a very slight swelling of the thyroid gland and a trace of exophthalmia. In the great majority of his 49 cases J Russell Reynolds (932) observed a satisfactory course. Saundby (637) considered that the outlook for a complete cure was bad Of 16 of the 32 patients for whom Hill Griffith (638) found notations concerning the later course, 8 were better after a shorter or longer (9 months to 6 years) period of time, or they were fully cured The rest remained unimproved during the observation period of 1 to 4 years. Among 12 Basedow cases about whose subsequent course Hale White (687) was able to get reliable information, 5 were still alive Among these was a 21 year old woman who was entirely cured after 3 years of the disease. The cure had already lasted 3½ years A 32 year old woman became able to work again, and a 13 year old girl, a 20 year old woman, and one of 34 years were greatly improved after a 2 to 10 year duration of the disease Single signs still remained Hale White estimated the average time in which the disease took its course to be 4 to 5 years in those cases which had a tendency to recovery. Gowers (1042) believed an estimated 25% of cures not too high He evidently had in mind a relative cure, for he added that complete cures were rare and that it could be expected more in mild cases and in the initial stages when cardiac disorders still were new and the goiter small. If all of the signs are strongly developed even careful treatment rarely achieves more than a moderate improvement, and in many cases even this fails

Prospects for further improvement are greater if the disease shows a definite remission Also, Gowers saw in the favorable living conditions of better-situated people a very essential supporting factor. Even in very severe cases one would not give up hope for improvement. One of his patients was in such a poor condition that he believed she would live only three months longer at the most After three years, however, she was much better and had married and become a mother Several such cases were known to him

Of 32 among 50 Basedow patients about whom Williamson, (1523)

In one case of a 30 year old man, an almost complete cure was achieved only after the disease had lasted, with slight fluctuations, for 12 years. This cure occurred, in fact, under quite unusual circumstances, namely in association with a nephritis of six weeks duration, azotemia and attacks of convulsions, to the extent that the goiter gradually became small and firm, the Basedow's disease signs gradually disappeared A certain irritability and a slight exophthalmia still remained He noted a similar but also less favorable influence in a second case of a 36 year old woman with pronounced Basedow's disease. Considerable improvement occurred after faradic treatment The vascular signs over the goiter disappeared; it became firm and all the Basedow's disease signs regressed to a minimum After discontinuance of the treatment the goiter began to grow again, the vascular signs returned, and therewith all the other signs and symptoms Only an acute nephritis with general edema and violent convulsions brought about hardening of the goiter and disappearance of the *bruit* A slight exophthalmia remained Later the Basedow's disease signs reappeared but to a lesser degree than before.

Syllaba (3065) stated that among 50 Basedow cases in which the course of the disease could be followed for a long time, 18 had improved and 13 were cured (did it last?). That amounted to 26% improved and 36% cures R. Stern (3065) very correctly reckoned as prospects for cure only those among his numerous cases which met the requirement of a long period of observation, and about which he could obtain follow-up information either by observation or by sufficiently detailed and trustworthy reports. Only 19 of the typical Basedow's disease met these requirements. Of these, 9 showed such an extensive improvement of their illness that they could almost be considered cured The goiter was still present although smaller in size and free from pulsation and from *bruit* The exophthalmia continued, with a single exception In favorably-progressing cases the disease had lasted once only 3 months, 5 times 1 to 3 years, once 8 years, and twice 11 and 11½ years respectively. The duration of this relative cure in 1 case had lasted already over 14 years, once over 10 years, once over 8 years, 4 times over 3 years, once over 2 years and once over 1½ years. Among the cases which he grouped as *Basedowoid*, Stern seems not to have observed so many relative cures even after many years.

v Noorden calls attention to the fact that Stern's statistics give, in general, much too unfavorable a picture of the outlook for cure among patients with Basedow's disease. They are the figures for Basedow's disease among poor people It can probably not be denied that in this disease, as in pulmonary tuberculosis and *diabetes mellitus*, the prognosis depends essentially on the size of the pocketbook (See also above).

French authors also differ considerably on the prospect of cure. Dumontpellier (823), assistant to the famous clinician Trousseau, saw many cases, and stated that he had not been able to recognize an actual cure in a single instance. In his lectures Charcot (815) expressed the conviction that, disregarding those rare cases in which the nature of the disease was most

Statements on such cases have been made by the experienced doctors we have mentioned above Přibram, Oppenheim, Chvostek, Hutchinson, Gowers, and G N Pitt, v Basedow (15 and 23), Graves (18), Romberg (39), A v Graefe (63) and Trousseau have made such observations Freidreich (191) saw a recovery in 2 cases. In each case debility and emaciation, extensive dropsy, tachycardia and enlargement of the heart gave reason to expect the worst E Payne (562) reported a 25 year old woman with severe symptoms She was so weak that she had to lie on a water bed After somewhat over a year the disease was almost completely cured *Sutton (418) described the severe case of a 13 year old girl who, in the course of the* disease, had an almost complete paraplegia, extensive bedsores, an uncountably weak pulse and who became so emaciated that death was expected *After she had* been in the hospital for nine months rapid improvement set in After four months the girl was discharged in fairly good health Bäumler (1512) mentioned a severe case of Basedow's disease, a man of about 30 who had enlargement of the heart and had become cachectic After a sojourn in the Engadine mountains, he was improved to such an extent that he was able to return to his office work Lanz (2306) made a similar observation in the case of a 38 year old woman Such observations have been made by v Rösslin (1450 and 3140) and Dinkler (written communication in the year 1900), in very severe cases in which death had been expected, but where a surprisingly *favorable turn occurred resulting in a cure A few examples which belong here have* been recounted in the cases with acute course (see §253 above)

Exceptionally, a cure or at least a considerable improvement has been *seen to occur* even after ten years of the disease (Kocher, R Stern, see above) Cases in which the permanence of this cure has been verified by a control continuing over a period of more than one year are very infrequent.

We have already mentioned one or two examples in the statements of Kroug (see above), R Stern, Hale White and Williamson In Tessier's (146) case the cure was said to have lasted for 25 years, and in Cheadle's case (881) for 20 years Přibram (2727) had seen a large number of patients, who after the disappearance of severe Basedow's disease, had remained under his observation from 20 to 25 years They had presented themselves *for observation from time to time*, and had *remained* healthy Oppenheim (2417) had seen the cures remain in 1 case for 22 years, in another for 14 *years, and 2 others for 5 and 8 years Permanent cures have often been seen following* a favorable turn in acute and rapidly progressing cases (see §252 above)

§259. Unusual circumstances sometimes bring about a turn for the better and a more or less complete cure, as we have seen in Kocher's case *After a 12 year course of the disease the appearance of nephritis with uremic* attacks initiated remission of the Basedow's disease (see above). Oppenheim (2417) once saw a striking improvement under the influence of icterus As a rule, icterus is *an extremely serious complication (see* §175 above)

§260. In the majority of cases pregnancy exerts an unfavorable influence on the course of Basedow's disease After delivery a temporary improvement occurs sometimes. Ominous developments can even furnish an *adequate basis* for the induction of an abortion (Theilhaber 1380 and others).

through personal sources or correspondence, gained reliable information on subsequent fate, a complete cure was ascertained in 5 (4 women and 1 man); this corresponds to 15.6%. The observation period varied between 5 and 14 years. An almost complete cure was determined in 2 more cases after an observation period of 7 and 17 years respectively. A satisfactory outcome occurred in 21 87% of the cases, if we omit the cases in which 1 to 2½ years had passed since their discharge, this amounts to 9 37%; 6 patients were unimproved after two to nine year periods of observation (18 75%).

Mackenzie (2537) estimated that "50% make a fairly good recovery, 26% drift on in a condition of chronic illness". Recovery, according to his experience, is very rare once the disease has lasted several years.

The subsequent course of Murray's 120 cases (2213) was ascertained in 40. Two remained unaltered Even in the most favorable cases, a completely normal condition was seldom attained. The term "cure" often meant only that the patients had nothing more about which to complain and they were able to perform the requirements of their calling. In this sense 9 are designated as cured Later 2 of these had slight relapses; 8 were considerably improved, 14 somewhat. Maude (2207) observed a few cases for many years and mentioned that, according to his experience, Basedow's disease patients seldom, perhaps never, completely recovered G. Newton-Pitt (2222) doubted a complete and permanent cure, but even in severe cases he did not give up hope entirely. He had 2 cases with advanced emaciation who later improved greatly.

Clark in Iowa (1546) treated 42 cases of Basedow's disease on whose further fortunes he was able to obtain information in the years 1892 to 1895. He described 18 as cured and 15 as improved W E. Quine (2871) in Chicago stated as an estimate that 60 to 70% of the cases were cured. Of the 56 Basedow patients whom J. M. Jackson in Boston (2968) had an opportunity to observe for 8 years, 42, that is 75% (with quinine treatment) were cured and 7 (12 5%) improved; four remained unimproved (7 14%) and two died (5 35%). According to Dana's (2163) approximation, half of the cases attain "a fairly comfortable condition of improvement" provided that they are subjected to proper treatment. A. Rufus Baker (2901) believed, from his experience based on 50 cases observed over a long period of time (an average of 9 years): "The natural tendency of the disease is toward recovery". Also, A. R. Elliott (3115) had gained the conviction that a large number of Basedow's disease cases under wisely regulated treatment were improved or cured, not only those with mild and chronic, but also those with more acute forms.

In isolated cases, an unexpected turn for the better may still occur even with extremely severe symptoms, as is vouched for by a number of reliable observers.

the signs of Basedow's disease disappeared rapidly Piqué saw the patient again one and one-half years after the operation, and was convinced of the permanency of the cure. In connection with Piqué's communication, Bouilly relates that he saw Basedow's disease disappear after an operation on the appendix Odeye also reviewed Tuffier's case of a 42 year old woman who suffered from a typical Basedow's disease and who came under his care because of multiple uterine fibroids Five months after bilateral castration the uterine fibroid was much smaller and the goiter had disappeared. A few months later nothing more could be felt of the fibroid Tremor and the other nervous signs had disappeared Only exophthalmia and a powerful pulsation of the cervical arteries remained In a case of Basedow's disease with an incomplete symptom complex, observed by Doléris (1204), all signs disappeared after a hysterectomy for a fibroma Vignard (1674) mentioned a case in which the Basedow's disease disappeared after the reduction of a uterine fibroid by electrical treatment Van der Linden and De Buck (1672) reported a 32 year old woman who had a tumor on the ovary for three years and suffered from Basedow's disease for several months The Basedow's disease subsided after an ovariectomy Also, in another of their cases the signs of Basedow's disease disappeared gradually following a hysterectomy In several of his cases Jouin (1330) observed that improvement or cure of Basedow's disease followed correction of a uterine condition almost immediately

Doléris rightly opposed a generalization from this observation He described a case from his experience in which local treatment of a uterine disorder produced no improvement in the Basedow's disease while general treatment had a favorable effect

§262. In isolated cases, suitable treatment of a nasal disorder can result in the reduction or disappearance of Basedow's signs as mentioned already (see §184 above)

The first observation on this was brought to the attention at the Naturalist's Convention in Strassburg in 1885 A 40 year old patient had a *rhinopharyngitis sicca* with extensive scab formation in the nose and the roof of the pharynx, greater on the right than on the left Furthermore, the woman had debility, weakness in the legs, palpitation, tachycardia up to 136, a painful sense of tension in the eyes, and slight exophthalmia v Graefe's sign was clearly developed, especially on the right No noticeable

subsided, the pulse rate became lower, and the patient felt stronger v Graefe's sign disappeared and exophthalmia decreased Two and a half years later a relapse

Soon afterward Hack (659) reported that a 17 year old girl with a mild but typical case of Basedow's disease had a nasal congestion caused by hyperplasia of the lower

B. Frankel's (761) patient was treated with direct electric current for a long time for relief of a rhinitis associated with a marked tachycardia and a large recently developed goiter The goiter diminished and the pulse rate became lower when evidence of nasal obstruction appeared and was treated by electrocautery The

Cases are also known, however, in which a favorable influence of pregnancy on the course of Basedow's disease has been observed with certainty.

v Basedow (15, p 227) had already made such an observation. Charcot (55), in 1856, observed such a favorable influence in the case of a woman from Piorry's division *In another case of Basedow's disease of an 18 year old woman, he believed* (113) that he could show a favorable influence of the pregnancy While treatment up to that time had remained ineffectual a definite improvement following the appearance of the first signs of pregnancy was noticeable, lasting well beyond the time of delivery The goiter still showed fluctuations in volume and, at times, *disappeared altogether* Exophthalmia remained to a slight degree Since then several similar observations have been described by Trousseau (in several instances), Huard (104), Corlieu (132), Moore (173), Souza-Leite (792), (Westedt (871), and Pinard (3170) G A Berry (807) reported a woman who had suffered from Basedow's disease for more than 10 years, [illegible]

[illegible] improved during pregnancy, 3 became worse, and 1 remained unaltered Mabille [illegible]

Her condition improved during each of 5 pregnancies Finally she was able to perform her household duties Nussbaum, in Warsaw (2105), stated that he had often been able to observe this favorable influence W Gilman Thompson (2773) saw definite Basedow's disease develop during pregnancy in 2 among 20 cases He added that several of his patients who became pregnant repeatedly in the course of a chronic Bas[illegible] (28[illegible] Bas[illegible] sen[illegible] goiter therapy was attempted, palpitation and tachycardia greatly improved during a pregnancy with twins Only the conspicuous exophthalmia remained This woman had 7 pregnancies including 2 abortions and 3 premature births

In view of these facts it is probably not permissible to regard this relationship as purely accidental, or to consider the observations inaccurate, as H W Freund did (520 and 543)

§261. Amelioration or cure of Basedow's disease has been accomplished *in many cases by correction or removal of gynecological difficulties*

Wettergren (1017) reported a 47 year old woman who had had Basedow's disease for over two years, and who at the same time suffered from bleeding from a uterine fibroid When a submucous fibroid the size of a man's fist was removed, the bleeding ceased, the anemia disappeared and the signs of Basedow's disease were considerably improved The influence in the following cases in which there was no bleeding leading to severe anemia is even more obvious Odeye's (1388) thesis gives an account of Picqué's patient who suffered from severe Basedow's disease with attacks of angina pectoris, and who had been treated unsuccessfully by Ballet for several years A uterine infection had remained unnoticed until it caused a disturbance A uterine fibroma was *found causing pressure* and *intestinal* obstruction After hysterectomy

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Soon afterward Hack (659) reported that a 17 year old girl with a mild but typical case of Basedow's disease had a nasal congestion caused by hyperplasia of the lower conchae. Noticeable improvement was observed in all of the Basedow's disease signs, the day after an electrocautery in the right half of the nose. The report does not indicate whether improvement continued.

B. Frankel's (761) patient was treated with direct electric current for a long time for relief of a rhinitis associated with a marked tachycardia and a large recently developed goiter. The goiter diminished and the pulse rate became lower when evidence of nasal obstruction appeared and was treated by electrocautery. The

condition remained unaltered for several weeks Improvement continued after electrocautery of the other half of the nose

A 45 year old woman observed by Muschold (1062) developed Basedow's disease at the beginning of menopause The exophthalmia was not distinct, and the lid signs were absent She suffered chiefly from violent palpitation and from headache at the base of the nose and over the forehead The examination showed hyperplasia of the right lower concha After removal of this structure the patient remained free from headache After the fifth day palpitation had disappeared The goiter gradually diminished, the other signs disappeared, and the woman regained her former weight.

Surukhi (1155) reports the case of a 20 year old woman who recovered from all symptoms of Basedow's disease after electrocautery of a thickening of the mucus membrane of the nose

Scanes Spicer (1378) observed a striking improvement in the Basedow's disease signs of a 17 year old girl who had had the disease for three years and who simultaneously suffered from obstruction of the nose Removal of the nasal polyps in several stages, brought improvement as the nose became freer

A 39 year old patient with Basedow's disease also suffered from attacks of hysteria Potts accomplished remarkable and lasting improvement of the Basedow's disease by treatment of a mucous membrane swelling in the nose.

The influence was less striking in a case reported by Winkler (1085) A 20 year old girl had definite Basedow's disease, and an obstruction developed causing a closing of the right half of the nose by palpillomatous tumors of the mucous membrane of the lower and middle conchae On the left, there was a large obstruction between the septum, the lower concha, and the floor of the nasal cavity There also was a swelling at the posterior end of the middle concha Exophthalmia disappeared almost entirely and the goiter grew smaller after operative removal of the growths, extirpation of a part of the lower and middle conchae on the left, and a rinse with a disinfecting solution Pulse rate went down to 90, and the nutritive condition improved considerably Skin pigmentation also disappeared However, in addition to the nasal treatment, absolute rest was imposed, a suitable abundant diet was initiated, and iron administered Three months later the improvement stopped, and tremor and nervous unrest had increased again. Electrical treatment and a sojourn in the country resulted in further improvement

Holz's (2514) 2 cases which were mentioned above must be recalled at this point Bilateral exophthalmia, lid signs, and adenoid growths in the nasapharynx were the only diseas
and the lid
the signs o

Stimmel (2122), before the Medical Clinic in Leipzig, presented a case in which there had been bilateral exophthalmia, tachycardia, and palpitations for at least 9 years. No lid signs, goiter or tremor were evident The exophthalmia disappeared after removal of the swollen nasal conchae It is a moot question whether the signs described can be designated as Basedow's disease

For comparison with Scanes Spicer's report (see above) G Stoker reports a man of 33 who had a soft, uncomplicated goiter and nasal polyps Although this goiter had defied all corrective measures, it gradually diminished during the electrocautery treatment of the nasal polyps Finally it disappeared entirely He has seen a second similar case.

Hamon de Fougery (2067) once saw a goiter disappear during treatment of a chronic rhinopharyngitis Thereafter he paid more attention to these relationships in more than 200 cases of goiter, and found a nasopharyngeal catarrh in all of his goiter pa-

tients. He treated this with gargles, and, when necessary, by cautery with chromic acid. He always noticed an effect on the goiter. In a few cases it disappeared entirely. In others it grew smaller

Cases are also known in which the treatment of a nasal disorder had no favorable effect on Basedow's disease This should not surprise us. In the previously cited cases (§246) of F Semon (863) a symptom complex developed (after a nasal operation) which probably must be considered an incomplete form of Basedow's disease

§263. A depressing emotional experience or shock usually exerts an adverse influence on the course of Basedow's disease and can initiate a relapse Cases are also known in which a joyful and happy mood brought about spontaneous improvement or remission of all symptoms

Rattner (2872) reported such a case A 21 year old woman had severe Basedow's disease on which therapy had no effect When seen again after she had withdrawn from all treatment for half a year, she had become much quieter, and had a brighter appearance Exophthalmia and goiter were reduced An engagement which she had wished for and which had now become a fact had brought about this change Information is lacking as to whether this striking improvement was lasting or not

§264. According to several observers Basedow's disease is in general more severe in men than in women (see also §92 above) A general application of this statement is not acceptable, however. There are exceptions

A v Graefe himself (§63) was led to this conclusion from experience Gowers (1042) also said, "for women the prognosis is more favorable than for men" Daubresse (540) believed that he could not detect any essential difference in the course of the disease in the two sexes He admitted that the prognosis for men seemed to him less favorable than for women Schmidt-Rimpler (1786) observed a brother and sister The Basedow's disease ran a rather mild course in the case of the girl. The brother, a student, died from it after a short time

Also, according to Kraus's (1870) experience the course of Basedow's disease is, on the average, more severe in men Mobius (2717) considered it as established that it "is more serious in men than in women" Likewise, Eichhorst (2820c) believed the prognosis for men generally to be more serious than for women

The opinion occasionally expressed that, in advanced age, probability is on the side of a less favorable course, is not established. It is certain, however, that Basedow's disease in childhood is, generally, more amenable to a cure But cases developing in the years of the climacteric also frequently are not severe

Syllaba (3065) reported that among 9 of his cases coming during climacteric 3 were cured and 4 were improved Only 2 remained unchanged

Sequence of Symptoms

§265. We depend upon the statements of the patients for the determination of the sequence of the symptoms in all of those cases not coming

under our observation at an early stage. Cautious criticism is in order on account of the excitability, forgetfulness, and suggestibility of many of these patients.

§266. In a large number of cases tachycardia is the initial sign. At the beginning often only a labile pulse is noticeable. Sometimes palpitation occurs from the beginning If it is absent the tachycardia may elude discovery for a long time (see §4 above).

Frequently irritability, fatigue, inability to concentrate and sleeplessness appear simultaneously with the palpitation. *Sometimes these symptoms* alone bring the patient to the doctor Such patients are often regarded and treated as neurasthenics. But if one investigates tachycardia carefully, active carotid pulsation, slight tremor of the hands, slight enlargement of *the thyroid, or one of the lid signs may be present. Oppenheim* (2417, p. 1370) even said "usually a neurasthenic or hysterical stage has preceded it"

Many patients, besides palpitation, had several nervous signs, rapid exhaustion under bodily and mental activity, hot flushes and perspiration.

Such patients must be carefully examined and kept under observation permanently. Cases occur in which the onset of Basedow's disease was preceded by tachycardia, palpitation, several of the nervous and vasomotor signs, and sometimes also by an unexplained emaciation of brief or prolonged duration.

Many of Kocher's patients (2197) first had a feeling of weakness, fatigue, excitement, restlessness, tremor, headache, sleeplessness or emaciation Only then did the palpitation become evident to the patient, and sooner or later thereafter enlargement of the throat and protrusion of the eyes became evident

In one case the symptoms described preceded the appearance of goiter and exophthalmia by 6½ years, in another by 3 years P J. Mobius (1886) had a patient whose *nervousness, tremor, and palpitation preceded the swelling on the throat by 5 or* 6 years Friedrichson (763) reported a 31 year old woman whose first symptom, emaciation, preceded weakness, headache, and vomiting by 6 months Palpitations came later Da Costa's 30 year old patient had no predisposition and had been *healthy previously The disease began with a sense of extreme fatigue, depressed* moods, nervousness, tremor and palpitation. Two months later a swelling in the neck became evident, and after another two months the eyes started to protrude Rosenblatt's (1071) case developed a tremor of the limbs directly after a shock Additional symptoms included dysuria, polyuria, polydipsia, hyperidrosis, urticaria and emaciation. Only later came tachycardia, palpitation, v Graefe's sign and finally goiter and exophthalmia

Cohn was able to draw definite conclusions concerning the sequence of the symptoms among 15 cases from Mendel's polyclinic In 6 cases, palpitation was the first sign, 2 cases first developed a headache which gradually increased Palpitation followed H. West (686) investigated 29 among 38 cases from St Bartholomew's Hospital and several other London hospitals Palpitation was the first symptom in 16

cases A 21 year old woman had palpitation as long as she could remember In several cases palpitation preceded the other symptoms by years In others the rest of the signs soon followed In 19 among 120 cases observed by Murray (2213) palpitation was the first complaint In 7 cases, nervous excitement and the other nervous signs all came at once In 4 cases the palpitation and exophthalmia were noticed at the same time In 3 cases palpitation and goiter, and in 1 case tachypnoea and tachycardia preceded the palpitation Among 47 cases designated by Stern (3060) as *Basedowoid* palpitation occurred in 8 cases an indefinite time before the appearance of the other symptoms

In rare cases the palpitation only comes after the other main signs are already plainly developed (see §238 and §267).

§267. In the majority of cases, goiter is the second chief sign to appear among the signs and symptoms characteristic of Basedow's disease (see §19 above). The exact moment of onset of the enlargement of the thyroid gland is usually difficult or impossible to determine. Sometimes, it is discovered by the doctor only when he palpates for it on the basis of other signs Often the patients become aware of it because their collars become too tight Many complain about a feeling of pressure in the throat even sooner, especially when they are lying down at night In rare cases the goiter only appears late, long after the rest of the symptom complex is complete (see §239 above).

On the other hand, cases occur in which the swelling on the throat becomes evident even before the occurrence of the palpitation. Slight tremor of the hands and other nervous signs, as well as moderate tachycardia can often be discovered by careful investigation.

Th. Kocher (3205) pointed out a sensitivity to pressure over the thyroid. This usually is not present in simple goiter. Characteristic vascular sounds in the form of systolic *bruit* about the thyroid arteries may be helpful in directing early suspicion toward the possibility of incipient Basedow's disease, when other signs have not yet developed distinctly.

We omit from consideration here the cases discussed fully in §242 and §243 where isolated signs of Basedow's disease or the symptom complex of a typical Basedow's disease complicated a simple goiter which had been present for some time

Roesner (340) among 6 and Glukinski (468) among 8 cases with a detailed anamnesis each found 1 case in which the goiter was the first sign to appear

Among 15 adequately studied cases assembled by Cohen (1031) from Mendel's polyclinic 4 cases occurred in which swelling of the throat was noticed first In the case of a 42 year old woman this had appeared 5 years before and had increased before each of her menses Then came violent tremor of the hands and hot flushes After a time other Basedow's disease signs appeared

Among 20 typical cases of Basedow's disease from the surgical division of the Hamburg Hospital, as reported by J Schulz (2118), enlargement of the thyroid

gland was the first symptom noticed by 3 patients Among Kocher's (2197) 80 cases the illness certainly began in 12 with enlargement of a previously normal thyroid Some time later the other signs appeared, once during pregnancy and once at the time of delivery In 2 of these cases, together with the thyroid swelling, nervousness, weakness, and headache appeared at the onset In one case, that of a 62 year old man, palpitation came only five years later, first in attacks, later continuously Protrusion of the eyes and the other signs of Basedow's disease followed. In 2 other cases, that of a 32 year old woman and a 20 year old girl, the acute Basedow's disease began with enlargement of the thyroid gland

Among 29 out of 38 cases, in which S. West (686) found data on the sequence in which the symptoms appeared, the goiter was noticed first in 8 cases In one of these it has been present for 20 years, while palpitation and exophthalmia had appeared only 4 years before Enlargement of the thyroid was the first noticeable sign in 43 of Murray's (2213) 120 cases Included in this count apparently are also the cases of *struma basedowificata* (see §243 above) Among 32 cases observed by Dock the goiter was the first disease sign observed In 12 other cases a goiter had preceded the appearance of the other signs of Basedow's disease by years (see §243 above)

H Moses (2864) reports a 41 year old woman Ten months after a hysterectomy, a nodule the size of a pea appeared on the right side of the throat It grew rapidly and developed into a horseshoe-shaped goiter A month later the other signs of Basedow's disease began to develop gradually

In the cases of Remlinger (2731), Campbell (2157) and Rudinger (2339) enlargement of the thyroid gland was the first sign of the onset of acute Basedow's disease (see §251 and §252 above).

In Story's (571) case the goiter had already been present for 5 years before palpitation occurred, in the case of Chvostek's (§252, 8th case) 30 year old patient for 4 years, in Yeo's (395) 35 year old patient for $1\frac{1}{4}$ years and in the case of a 41 year old man observed by Féréol (335) $\frac{3}{4}$ of a year The exophthalmia in these cases preceded the palpitations Similar cases are reported by Markham (70), Moreau (175), Wilks (250), Chvostek (332 and 399) and Mobius (495)

Chrétien (753) in his thesis reports a peculiar case A previously healthy 36 year old seamstress developed a goiter and frequent vomiting Vomiting did not cease after the operative removal of the goiter The character of the patient changed She became irritable, then the eyes began to protrude Only then the palpitation, tremor of the hands, and other signs of Basedow's disease set in The goiter did not continue to grow

§268. It is unusual when lid signs and exophthalmia, or the former alone, appear as earliest manifestations, noticed by the individual or those around him Nevertheless, the number of cases of this sort recounted in the pertinent literature is not small Thorough, careful examination can also discover other signs as a rule, which, even if only minimal, tend to guide the diagnosis in the right direction.

A 21 year old soldier under Chvostek's observation (399, 20th case) developed an unexplained gradual protrusion of both eyes as the initial signs of disease A small rightsided goiter had been present for a long time There was no complaint of palpitation The pulse rate was 92 at rest and 100 after brief exercise v Graefe's sign was present. Involuntary blinking was infrequent. A 59 year old woman whom

Roesner reported (340, 5th case) stated that the eyes had protruded first At a subsequent examination "no trace of exophthalmia remained". A 19 year old girl, observed by Samelsohn (442), had a rightsided exophthalmia as the first sign (see §32 above) In E Payne's (562) case, Kahler's (775) 43 year old patient, and Joffroy and Achard's case (950) as well as in one of Drusmann (1035), exophthalmia preceded the other signs of the disease A 5 year old boy observed by Demme (964) developed acute Basedow's disease following the appearance of exophthalmia (see §253 above). In other cases of children protrusion of the eyes was the first abnormality noticed (see §297 below) A case reported by J B Nias (1063) was a 33 year old laborer whose staring expression of the eyes was noticed two weeks after an epileptic attack Gradually exophthalmia and lid signs became more distinct, but, in the course of several weeks, went away again In the case of an asthenic 31 year old man reported by Barella (1171) leftsided exophthalmia and lid signs appeared rather suddenly Following this, a typical Basedow's disease gradually developed The exophthalmia remained unilateral. A 24 year old woman observed by Hinshelwood (1853) had a violent shock followed by a left hemicrania and a leftsided exophthalmia, then exophthalmia appeared on the right side Six months later lid signs and tachycardia were also present The patient became excessively nervous There was no palpable goiter A 47 year old male under the observation of Gérard Marchant (Herbet 1973, p. 151) developed a protrusion of the left eye as the first sign of disease Since general and local disturbances were lacking, Galezowski believed himself to be dealing with a benign orbital tumor One year later the right eye began to protrude Then the exophthalmia increased rapidly and became greater in the right eye than in the left Two years later this previously quiet man became greatly excited There was sleeplessness, palpitation, and tremor Finally an enlargement of the thyroid gland was discovered A similar case came under the observation of A Trousseau (2246) In the case of a 42 year old nervous, emaciated woman one eye began to protrude from its orbit without any known reason An oculist assumed a malignant tumor, and proposed an operation Trousseau also did not venture to diagnose this case as Basedow's disease although tachycardia was present, since the exophthalmia was onesided This exophthalmia fluctuated in degree Three years later a swelling of the thyroid gland occurred and the tachycardia became more extreme Cachexia also increased In the similar case of a 29 year old woman with rightsided exophthalmia and distinct lid signs Gifford (2666) had assumed the presence of a benign orbital abscess The nervousness and attacks of palpitation were ignored at the time A 22 year old woman observed by Campbell, Posey, and Swindells (2433) noticed leftsided exophthalmia as the first disease sign after a shock In the first examination, two years after the appearance of the exophthalmia, a small symmetrical goiter and tremor of the hands was discovered The pulse rate was 82 The girl had always been very nervous, blushed easily, complained of hot flushes, and had occasional palpitation In one of the cases reported by Berger (1088 and 2146) protrusion of the eyes was the first of the cardinal signs following a more or less prolonged troublesome epiphora (see §81 above) Slight exophthalmia appeared during pregnancy in the thirty-eighth year of life in a case observed by Christens (2473) This was the first noticeable disease sign Six years later, during pregnancy, a swelling appeared on the front of the throat After that all the signs of Basedow's disease came in typical form H Moses (2864) reported a case from Carre's clinic, associated with a hysterectomy During the subsequent treatment a protrusion of the eyes remained noticeable The woman felt weak After various fluctuations the condition became worse and a definite goiter developed Resection of the goiter

brought lasting improvement I call attention again here to Uhthoff's observation (2890) cited above (§91) A 72 year old woman had a bilateral protrusion of the eyes *which developed rapidly to a high degree as the first* disease sign. It was soon complicated by a purulent keratitis of both eyes which caused the woman to visit the eye hospital Palpitation and a moderate tremor appeared only during the period of observation

Among 8 cases of Basedow's disease observed by Gluzinski (468) with an exact anamnesia there was one in which exophthalmia preceded the other signs. The same was true in 2 among 15 cases collected by Cohn (1031), in 3 among Riedel's 50 cases (K Schultze 2750), *in one of 24 cases from the Göttingen Medical Clinic* (Runge 2228), and in 3 among Kocher's (2197) 80 cases. In one of these cases, according to the statement of the patient, the exophthalmia was noticed 2 or 3 years before goiter and palpitation At about the time the eyes protruded many patients became excited, trembled at the slightest emotion, became easily fatigued, and began to grow emaciated In one of Kocher's cases, a 27 year old woman, the disease began with headache, nervousness, tremor and a "staring look" Perhaps there was a slight exophthalmia with lid signs After a year, exacerbation of these manifestations and swelling of the throat was noticed, soon afterward tachycardia and palpitation set in

In 29 out of 38 cases, in which the sequence of the symptoms could be reliably ascertained, S West (686) found 5 cases in which exophthalmia was the first disease sign to be discovered In the case of a 28 year old woman it preceded palpitation and thyroid enlargement by three years, in another case exophthalmia came first by three to eight months In 5 among more than 30 cases observed by H Mackenzie (918) protrusion of the eyes had been observed for from one to several years before the appearance of the other signs Among Murray's (2213) 120 cases exophthalmia was the first sign in 4 In 4 other cases exophthalmia and palpitation were noticed at the same time In 1 case exophthalmia and goiter came first

§269. We have already become acquainted with many cases in which the lid signs, bilateral or unilateral, were the initial stage. I refer to the cases of S. Snell (737, §47, and §246), Cerise (Monthus 3004, ibidem) and Polack (3171, §47) and some others Besides the abnormally wide gape of the palpebral fissure, which first greatly impressed the patients, other Basedow's disease signs also were discovered during the first examination

Th Kocher (3250) called attention to the fact that when an object, which is held in the median plane, is moved up and down rapidly and the patient is told to follow it with his eyes, a momentary spasmodic retraction of the upper eyelids can frequently be observed.

§270. Sometimes leakage of tears is the first disturbance causing the patient to seek medical advice. In such cases, there is usually a local treatment with astringent eye drops, probing of the tear ducts, etc , without any success. A more thorough examination sometimes also reveals tachycardia, sweating, slight tremor, and other nervous signs, perhaps even the lid signs. In isolated cases, however, copious weeping or even attacks of dakryorrhea lasting for months or years precede the development of pronounced

Basedow's disease signs. Then the significance of the flow of tears becomes difficult to interpret (see §81 above).

In isolated cases edema of the eyelids is bilateral Sometimes, however, such edema is unilateral or tearless, and lid signs or tachycardia and a fine tremor represent the first noticeable sign of a developing Basedow's disease (see §221 above).

§271. In rare cases a peculiar enlargement of the vessels on the anterior surface of the orbit, without inflammatory changes in the conjunctiva, is an initial sign impelling the worried patient to consult the doctor, especially when combined with an uncomfortable sensation in the eyes (see §83 above).

Topolanski (3197) recently called attention to a manifestation on the anterior surface of the bulbus not previously noticed. It consists of a wide pale, reddish or bluish-red band corresponding to each one of the four rectus muscles, each band 2½ to 3 mm in width stretching toward the cornea and disappearing about 2 mm before reaching it. Over these bands run enlarged veins with very fine branches, often communicating and rejoining one or two small vessels. Thus, there arises, directed toward the cornea, an "erythematous cross" which leaves a ring free around the cornea Between the separate bands the surface of the eyeball is mostly porcelain-white or filled with delicate blood vessels. This cross disappears only when exophthalmia appears or lasts a long time and the whole surface of the eyeball again appears uniform. The true nature of this manifestation can easily be misunderstood when other Basedow's disease signs are still lacking Local therapy is powerless.

Topolanski reported 2 such cases, on the basis of the manifestations described he expressed the opinion that it related to the onset of Basedow's disease In 1 case a slight thyroid enlargement on the right was evident which the patient had not noticed After continued observations, there appeared, within a relatively short time, all the signs of Basedow's disease including the cardiovascular signs in particular and finally the bilateral exophthalmos Ohlemann[1], himself suffering from Basedow's disease, observed on his eyes, which were only slightly protruding, an enlargement of the episcleral and anterior veins of the conjunctiva These were not arranged distinctly in the form of a cross, and were more strongly developed toward the median than toward the temporal side He believed that this development could be attributed to a congestive hyperemia, caused by pressure of the goiter on the vena jugularis interna

§272. We have already emphasized by a description of the symptomology and by a series of examples (see §172, and §173 above) that, in certain cases, gastric disorders, diarrhea, and vomiting open the scene or appear among the first signs of Basedow's disease.

[1] Archiv. f Augenheilk. LXV, 1910, p. 43

A 31 year old woman reported by Friedrichson (763) showed an unexplained rapid emaciation, the first noticeable sign of the onset of the disease; only afterwards came feelings of weakness, headache, and vomiting. Half a year later palpitation and the other signs appeared. A similar course has been observed by others in unusual cases.

§273. The appearance of a brownish pigmentation of the eyelids can attract attention in a few cases even before other signs of Basedow's disease are clearly developed (see §205 above).

§274. Exceptionally, the disease begins with a rise in temperature (see §225 above) In a case observed by Henriesson (2838) the body temperature rose without known cause to 41° Then came general debility, diarrhoea, and epistaxis A few weeks later goiter, tachycardia, and exophthalmia appeared A case of Basedow's disease in childhood was reported by R. Forster (893) This disease began with a temperature rise and an obstinate diarrhoea (see §290 below).

Sex

§275. That the female sex is predisposed to Basedow's disease to a degree is well known. Statements of the various authors as to comparative numbers of the two sexes in the morbidity differ, however, according to nature and extent of their observation material.

Hardy (546) stated that the disease was primarily found in females In J Russell Reynold's (932), Clarke's (1546) and Gordon Holmes' (1325) collections more than 49, 47 and 88 cases respectively were women, about 98% The ratio is reduced by Gayne (1720) to 1 75 1 Indeed the relatively small series of two observers, Stoffela (570) in Vienna, and the Swiss Hermann Muller (728), contained more men with Basedow's disease than women The former estimated the ratio as 3:2. Chvostek had an unusually large proportion of men among his Basedow's disease patients. This proportion is, however, quite exceptional It by no means applies to Austria and especially to Vienna, as is seen by the numerous cases, and especially from the wide range of observations on typical and incomplete cases of this illness available to R Stern (3060) from the first medical clinic in Vienna

Eichhorst (2820c) states that he was struck by the relative frequency of the illness in men during his work in Switzerland The numerical reports concerning such cases in the Zurich medical clinic, however, do not support these statements (see below) Perhaps men were more numerous among his private patients

Since only rather large numbers ensure a reliable conclusion I have noted sex and age in all 3800 cases cited in all the literature available to me, as well as my own cases. Of these, 3210 are female and 590 male. This gives a ratio of 5.44:1. An approximate average is obtained from the majority of those series of observations which extend over a large range of material.

Buschan (1181) reckons, on the basis of 980 cases assembled by him, a ratio of 4 6.1 A. v. Graefe (192) found 6.1, Romberg and Henoch (39) 5 75.1, Withusen (73) 5 25.1. On the basis of 91 cases in the Leipsic medical clinic (Roper 1911), the proportion of female to male Basedow patients proved to be 6.1, on the basis of 45 cases of the Breslau Medical Clinic, Donchin (2644) gives the ratio as 6 5:1 On the basis of 50 cases from the Jena surgical clinic Kurt Schultze (2750) gives it as 6 14:1 Garre (2946), on the basis of 35 cases as 6.1 L Bruns' (2268) 24 cases show a ratio of 5.1, R. Stern (3060) of 96 cases from the first medical clinic in Vienna, 6 38·1 Eichhorst (2820e) at the Zurich Medical Clinic treated, from 1884–1906, 40 cases of Basedow's disease among 35,475 patients Of these, 31 were female and 9 male Many more men than women were received, the ratio being 22,450 to 13,025, the proportional figure for the male patients was 0 04 and for the female 0 24, that is, 6 female to 1 male Th Kocher's (2197) extensive case histories give a ratio of 4 5 1

The collection of Basedow's disease cases from several other centers in Germany shows a larger proportion of females Among Mannheim's (1222) 47 such cases from the Mendel's Polyclinic in Berlin 44 were women and only 3 were men, giving 14 67:1 Among the 46 cases collected by Upshoff (2131) from the medical polyclinic in Marburg only 3 were male Basedow's disease cases, the ratio being 14 33:1 The ratio of Mooren's (1759) 58 Basedow's disease cases was 13 5.1 On the other hand, the preponderance of the female cases was less prominent among Passler's (1362) cases from the medical polyclinic in Jena. The ratio was 2 87:1

Among Landstrom's (2849) 52 cases from the Seraphim Hospital in Stockholm, the ratio of female to male was 9 4·1 If, from the casuistic of J. Holmgren (3138), which comes partly from the same institution, one considers only cases which can be regarded as typical or as incomplete Basedow's disease, the ratio of the two sexes was 4 8·1 N v Szontagh's (1919) 82 cases observed in New Schmecks (U Tátra-fured), came chiefly from Hungary and Lower Austria. Half of them were Jews (see §298 below) The ratio for the two sexes was 4:1 In England, the female sex seemed predisposed to Basedow's disease to a much higher degree Among 13 observers whose statements permitted a conclusion only 3 offer figures of the ratio approaching the values given above Taylor (59) 4:1, Gowers (1042) 5:1, and Berry (807, Edinburgh) 5 67.1 The latter added, correctly, that the proportion of women suffering from the disease might possibly be much larger still, since perhaps male cases are recognized earlier because they are rarer, and, usually, severe (see §264 above) All the observers, and especially those who had access to large numbers of cases, note a conspicuous predominance of the female sex. An average of a total of 660 cases shows a ratio of 23.8:1 That corresponds to a predominance of the female sex of 94 75%.

Among 51 cases observed by S West (687) there is a ratio of 16 1, J Russell Reynold's 49 cases show 48 1, H Mackenzie's (2994) 212 cases show 10.78.1 (6 years earlier

(2205) only 52 cases showed 7 67·1), Gordon Holmes' (1325) 88 cases show 43:1, Gilman Thompson's (2773) 80 cases show 8:1, and Murray's (2553) 180 cases show 17.1

In the United States the various statistics show results varying very widely from each other.

Cases collected by L Fiske Bryson (1025) show the ratio of female to male patients as 2 75:1, Eshner's (1715) 227 cases as 4 5.1, Pepper's (563) 68 cases as 4 67:1, Frank Billings (2806) 61 cases as 6 62:1, Dock's (2641) 32 cases as 9 67:1, Cobb's (1548) 14 cases as 13:1, Jackson's and Mead's (2968) 85 cases as 16:1, and Clarke's (1546) 47 cases as 46:1.

Although Basedow's disease, especially in its mild and incomplete forms, is not rare in France and especially in Paris, few series of observations are available from which reliable conclusions could be reached about the proportion of morbidity of the two sexes.

Trousseau (219) stated the figure as 5 25:1, Renault (930) as 6:1. 12 cases of F.de Ranse (675) show a ratio of 3:1, 15 cases of Boinet (1695) 2.75:1, Gayne's (1720) 11 cases 1 75:1. Hardy's Basedow's disease patients were almost all women.

Among 106 Basedow cases observed by Krough (700), all of whom came from regions on the Gulf of Finland, were 87 women and 9 men, a ratio of 4 58:1 Sokolowski (3192) counted 120 women and 12 men (10:1) among 132 such cases treated by him in Riga. Ninety four of the women were married and 26 unmarried. 15 cases collected by Gluzinski (468) in Cracow show a ratio of 11.75:1

The extent to which the female sex is predisposed toward Basedow's disease is shown from the family histories of many cases which we cite when discussing hereditary relationships.

It should also be recalled, as well known to all observers in goiter regions, that the female sex has a much greater tendency toward goiter than the male sex.

R Virchow (200) furnishes a number of statistical contributions to this subject from earlier times Rossander[1] reports that in Dalekarlien, the only goiter region in Sweden, every third or fourth woman had a goiter Among 73 goiter patients visiting the surgical polyclinic in Stockholm in four and one-half years, there were 71 women and only 2 men In other locations this preponderance of the female sex was not found The ratios were between 8:1 and 5:1.

It must also be pointed out that, at the time of menstruation, a slight enlargement of the thyroid is sometimes perceptible. Goiter not infrequently begins during pregnancy or receives new stimulus at that time.

[1] Verhandlung des X. internat mediz, Kongresses in Berlin, 1890 vol. III, section 7, p. 63.

Age

§276. Basedow's disease has been observed in persons of all ages, but its frequency varies in different age groups. The case material which I have collected from the pertinent literature and from my own observations covered altogether 3477 cases where the ages were noted. These cases can be grouped *according to age and sex as follows:*

Years	2½	3½	4½	5	5½	6	7	8	9	10	10–15
Female		2	2	3	1	1	5	5	7	14	105
Male	1		1	2			3	3	1	4	24

Years	16–20	21–25	26–30	31–35	36–40	41–45
Female	405	511	479	382	320	271
Male	70	89	61	68	54	51

Years	46–50	51–55	56–60	61–65	66–70	Over 70
Female	186	123	65	31	10	6
Male	56	26	17	7	3	2

The sum total, as shown by these tables, amounts to: Female 2934 and Male 543. The ratio of the sexes equals about that resulting from counting a still larger number of cases in the preceding paragraph—i e., 5.4:1

From childhood to the end of the 15th year we find 184 cases of illness: 145 in females, and 39 in males These 145 cases comprise only 4.94% of all female cases of Basedow's disease, but the 39 cases in male children make up a percentage of 1.18% of all males with this disease. Thus, it is evident that among males a relatively large proportion of the cases occur during childhood The preponderance of females among those having Basedow's disease in childhood is much less conspicuous than during the middle years of life. The ratio of girls to boys amounts to 3.72:1 If we include the first ten years it is 2.67:1. Since the calculation is made from a relatively large number, chance is fairly well excluded

Among females, most of the cases occur between the ages of 16 and 40. In our list this group makes up 2097 of the cases or 71.4% of all the cases of Basedow's disease in females Among males the number of cases during this period of life is 342, or 62.6% of all the boys and men with Basedow's disease. The sex ratio of the morbidity index during this period of life is 6:1.

The ratio according to age group at 5 year intervals is as follows, for females and males:

Age group (years)	Ratio
16–20	5.78:1
21–25	5.74:1
26–30	7.85:1

Age group (years)	Ratio
31-35	5 67:1
36-40	5 9:1
41-45	5 31:1
46-50	3 32:1
51-55	4.73·1
56-60	3 82.1
61-65	4 43:1
66-70	3.33·1
over 70	3.1

The distribution of the disease among the separate age-groups as percentage of the sum total of Basedow patients in the two sexes is as follows:

Age group (years)	Females (per cent)	Males (per cent)
16-20	13 8	12 9
21-25	17 4	16 4
26-30	6 3	11 2
31-35	13	12 5
36-40	11 25	9 9
41-45	9 23	9 4
46-50	6 34	10 3
51-55	4 19	4 5
56-60	2 21	3 1
61-65	1 05	1 3
66-70	0 34	0 5
over 70	0 2	0 37

The first of these two tables makes evident that from the 45th year on the preponderance of cases of Basedow's disease in females begins to diminish, and the proportion approaches that in the childhood age group, which is 3 79:1 The years of the climacteric are associated with a slight increase. The second table makes evident that among men the maximal figure, even in youth, falls between the 20th and 35th year Beyond the 45th year the percentage of men with Basedow's disease does not greatly exceed that for women This percentage for men is 20 44% compared with 14 34% for women The high figure found in our statistics for the cases of the disease in the age group from 16 to 40 among women is reflected with remarkable regularity in the calculations of single observers.

Buschan (1181), among 407 female Basedow's disease cases counted 306 in the above mentioned age group or 75 7% Murray (2213) similarly counted 65 among 88 women, making 73 86%, Stern (3060) among 83 female patients, so counted 65 or 78 31%; Roper, (1911) among 78 women, counted 63 or 80 77%, Kocher (2197), among 64 female patients, counted 50 or 78 12% and Uphoff (2123) counted 31 or 72 09% among 43 women

Within these age groups the illness is found most frequently between the 20th and the 30th year.

Our summary contains 930 cases amounting to 33 74%, that of Buschan 35 38%, Murray's series 37 5%, Stern's series 33 73%, Roper's series 53 84%, Kocher's series 26 36% and Uphoff's series 39 53%

The percentages of males shown in our statistics do not generally exceed those of other authors with fewer cases. Only Buschan's ratio is almost the same. Beyond the 40th year of life Basedow's disease cases among men amount to 31 8% as compared to 17.7% among women Eichhorst (2820c) said, without giving definite figures, Basedow's disease among women occurs most frequently between the 15th and 35th years, among men, on the other hand, it develops in later years.

R. Stern (3060) calls attention to the fact that many incomplete cases of Basedow's disease especially so-called goiter heart and the form called *Basedowoid* develop before the 21st year of life, while by far the greater portion of typical Basedow's disease arises between the 20th and the 40th year of life.

Of Stern's own 96 cases 21 were between the 11th and 21st year of life 17 girls and 4 boys, 59 were between the 21st and 40th years of life 50 women and 9 men, 16 were over 40 For the 3 age periods the percentages were 21 77, 61 46, and 16 77% *of all the cases In the majority of these cases the onset of the illness could not easily* be determined precisely If we accept this age of onset as the criterion for the distribution, the first category might increase considerably at the cost of the second

J Holmgren's (3138) 29 cases included many incomplete cases, especially "goiter heart" *There were 14 or 48 28% between 21 and 40, and 4, or 13 79% between 41* and 70 years of age

Kroug (2700) believed, on the basis of his experience, that the occurrence of Basedow's disease among married women is rather evenly distributed throughout the third and fourth decades and again over the years of the climacteric and the following years Among girls, the second and third *decades were important Among men, most of the cases occurred in the* second, third and fourth decades

Basedow's Disease in Childhood

§277. The preceding paragraphs have demonstrated 5 3% of all cases of Basedow's disease occurring in childhood (up to the end of the fifteenth year of age) This includes 184 out of a total of 3477 cases Thus, Basedow's disease in childhood is by no means so rare as is often supposed However, many of the cases are mild A peculiarity of Basedow's disease in childhood *is that it is usually not severe (see §296 below).*

Among the 184 childhood cases 11 came in the first five years of life, 44 in the second and the rest, 129 cases, in the third. With advancing years the morbidity from Basedow's disease also rises rapidly in childhood from 6% to 24% and 70%.

In childhood the preponderance of the morbidity among females is less conspicuous. The ratio changes more and more with the advancing years to the disadvantage of the girls as shown in the preceding paragraphs.

Several cases have been excluded from our list which were included uncritically by Steiner as cases of Basedow's disease in childhood and which were included by many other authors[1] without evaluation of the original data

Adult cases have been omitted in which it is stated in the anamnesis that the first symptoms of the disease go back to childhood, but a reasonably careful determination of the exact age was not possible

In general one can say that the symptom complex of Basedow's disease shows the same characteristics in origin and course, in children, as in adults. As a rule, however, it is less rich in signs and usually follows a milder course.

§278. In connection with the latter circumstance it may be noted that tachycardia in children is usually of lesser intensity that in adults, although, usually, a higher pulse rate is found in healthy children than among older persons While the pulse rate of adult Basedow's disease patients in at least half of the cases amounts to more than 120 per minute (see §2 above) hardly a quarter of the cases among children show a pulse rate above 120.

Among 130 childhood cases in which data on the pulse rate are available, only 23 show rates between 125 and 150 It went above 160 in only 5 cases. Once a pulse rate of 220 was noted in the case of a 12 year old girl

These cases with marked tachycardia were, with few exceptions, severe illnesses. All of the fatal cases are in this group. Usually, these cases showed distinctly a forceful apex beat, rapid pulsation of the chest wall in the region of the heart, and extension of the cardiac dullness.

The subjective symptom of cardiac palpitation was noted in 46 childhood cases. Perhaps it appears less frequent only because, when it is not very distressing small children do not complain of it. In several of these cases the forcefulness of the heartbeat is emphasized especially In one case the absence of palpitation was mentioned specifically.

In a few cases pulsation of the carotids was particularly noticeable, as in Batchelor's (2457) fatal case of a 3 year old girl, Demme's (964) rapidly deteriorating case of a 5 year old boy (see §253 above), Dusch's (103) case of a 13 year old boy and Fr Kraus' (984 and 1871) case of 13 year old girl

In v. Dusch's case as well as in Chvostek's (333) case of a 12 year old girl a rapid pulsation of the enlarged thyroid arteries was apparent. Excessive

[1] A case of Déval (Traité des maladies des yeux, Paris, 1862, page 819, concerning a 2½ year old child, as well as cases of Louis (2), Horn (2), Demours (7a and b). Cases described by more than one author have been counted twice, too.

pulsation of the abdominal aorta was noted by Fr. Kraus in the case of the 13 year old girl just mentioned. With a regular pulse rate of 85 to 90 at rest, she also had attacks of tachycardia up to 140 beats per minute associated with severe palpitation. The pulse in children with Basedow's disease is usually shallow and weak. Demme was impressed by the pressure of the pulse in the cases of the five boys mentioned above. In the case of a 12 year old girl whose history was contributed by Rahel Hirsch (3135), the rather high blood pressure of 110 to 190 mm. was found. An arrhythmia of the pulse has been observed in only a few cases.

§279. The goiter in children is usually not very massive; it is of soft elastic consistency, and, in the great majority of cases, rather symmetrical.

Among 126 cases which offer data concerning the goiter, the enlargement was in 5 cases in the left lobe or in the left lobe and the isthmus. In 9 cases it was greater on the right than on the left. In 1 case it was predominantly on the left.

In 12 cases the goiter was described as large, with a neck circumference of 13.5 to 37 cm and an average of 33.25 cm. In 13 cases it was rather large (27 to 29 cm), in all other instances the enlargement was moderate or scarcely noticeable.

In a case observed by Trousseau, a 14½ year old boy, the goiter grew rapidly to such a size that it caused choking attacks (see §253 above). In Kocher's (2179) case of an 8 year old boy the goiter increased rapidly in size and caused a tracheal stridor (see §253 above). In a rather severe case described by Hock (1323), an 8 year old girl with a large goiter, stridor laryngeus could be heard.

A. S. Smith (680) reported a periodic enlargement of the thyroid gland in the case of an 11 year old boy.

One evening, a swelling of the thyroid gland suddenly occurred. The next morning it had almost disappeared, but the next evening it occurred again, then these changes recurred several times. A loud systolic whistling *bruit* was audible over the goiter. There were also tachycardia, palpitation, a temperature rise to 38.6°, and a considerable enlargement of the spleen. Quinine produced an improvement after ten days, and the enlargement of the thyroid gland was permanently cured. A. S. Smith considered the case an unusual form of malaria.

Vascular signs over the goiter have been noted in not a few cases. Probably not enough attention has been paid to them.

A more or less loud whistling *bruit* was audible in 6 not very severe cases, 3 times concurrent with a thrill. Among these were 2 acute cases of H. Müller (835) and of Kocher (2197, see §253 above). Pulsation was observed 9 times. These included 2 acute but favorably ending cases, those of Trousseau (94) and of Demme (964, see §253 above). The others included 3 severe and 4 incomplete cases. A definite thrill could be detected in 3 more cases in which the eye signs were absent. In 3 cases the absence of vascular signs was expressly stated.

A severe case, ending fatally after ten weeks, was observed by Schwekendiek (569). This 2½ year old boy's thyroid gland was not noticeably enlarged In 5 *other well-developed cases the goiter was not demonstrable* during the entire period of observation

Similar cases were those of V Mathes (2541), a 10 year old boy; of Lewinberg (2405), two 10 year old girls, of Hingston Fox (1196), a 12 year old boy; and of E Cecil Williams (2447), a 12 year old girl

A 2 year old girl was the youngest of 5 children of healthy parents. Four of these children *developed signs of goiter heart, as reported by Beyard Holmes (1731)* There was no enlargement of the thyroid, but only tachycardia and tachypnoea

The absence of a discernible goiter occurs as often in children as in adults with this disease, in about 4% of the cases (see §239).

§280. Exophthalmia, the least constant of the cardinal signs, is more frequently absent in children than in adults. Among 132 cases for which data on this point are available, no protrusion of the eyes was discernible in 52 or 39 4%. This sign is absent in 23 2% of all cases of Basedow's disease (see §241, above)

Exophthalmia in children reaches a high degree only rarely. In 37 cases it was moderate or distinct and in 31 cases it was slight. It was extreme in only 12 cases, that is, in 9 1% These were all severe cases. Five ended fatally and in 1 case death was expected.

Lid signs seem to be absent still more frequently among children with Basedow's disease It is probable that suitable attention has not been given this sign in many cases Without exophthalmia the lid signs were always absent With a minimal or medium grade of exophthalmia, two lid signs were noted in 9 cases A wide gape of the palpebral fissure was noted in 5, v Graefe's sign was distinct 5 times and equivocal once Among the other 48 cases of this category, it was either absent or not mentioned In 12 cases with protrusion of the eyes an increased gape of the palpebral fissure was always present. In 4 instances, v. Graefe's sign was also present.

In the severe case mentioned by Schwekendiek (569), a 2½ year old boy developed abscesses of the cornea a few weeks before death, first on the left eye then on the right also These abscesses were followed by complete suppuration of both eyes (see §90 above)

Mobius' sign has been observed in only one case reported by Walitzki (2134), in a 5 year old boy with typical and favorably progressing Basedow's disease. Twice the absence or insufficiency of convergence was expressly stated. Otherwise this sign seems not to have been sought or could not be tested.

§281. Tremor is encountered much more frequently among children with Basedow's disease than among adults. Sixteen cases must be excluded

from the start because they were studied before the time when P Marie pointed out the almost constant presence of the characteristic tremor (see §95 above). Nevertheless, the fact that the tremor was not mentioned in any of these cases is an indication that it was not very pronounced Otherwise, it would not have escaped the attention of the observers, some of them very good, such as Romberg, v. Dusch, Demme, Chvostek, Jacobi, Trousseau, and others. Among the other 116 cases, the presence of more or less tremor was noted in 60 instances. This signifies 51.72% of all the cases coming under consideration We may assume with certainty that it occurred in a number of these cases, but was not noted or recorded Absence of tremor is expressly stated in 16 cases, one of these the severe and fatal case of a 3 year old girl (Batchelor 2457)

In the case of a 14 year old girl tremor of the whole body was so severe that she found it difficult to stand (Stegmann 2582) Tremor extending to the lower extremities was observed in 3 cases In 3 instances tremor of the tongue was noted

§282. Disturbances of the appetite are noted occasionally In a few instances, appetite was described as good Twelve children with Basedow's disease suffered from diarrhea and vomiting. With the exception of Stern's incomplete case (3060) of an 11 year old girl, all were severe forms of the disease; 4 of the cases ended fatally. The diarrhea usually occurred in the later stages of the disease and hastened death. In Batchelor's (2475) case, a 3 year old girl suffered from uncontrollable vomiting shortly before her death In the case of Schwekendick (569) mentioned several times, the illness began with loss of appetite Shortly before death, diarrhea and vomiting occurred In the case of a 10 year old boy whom R Förster observed, the illness began with an obstinate diarrhea which ceased during the subsequent course of the disease

§283. Tachypnoea is not infrequently noted among children with Basedow's disease Sometimes it amounts to actual breathlessness without any apparent mechanical cause It is either continuous or precipitated by the slightest exertion Sometimes dyspnea occurs in attacks

More or less shortness of breath is mentioned in the history of 14 patients In 4 instances it complicated rather severe, fully developed forms of the disease ending with cure or improvement, as in the cases of Bootz (695), a 4 year old boy, Stegmann (2764), a 14 year old girl, Kalm (627), a 13 year old girl, and Walitzki (2134), a 5 year old boy Six cases were mild and the symptom complex incomplete Jacob's (336) case, a 10 year old girl, W Pepper's case (391), a 15 year old boy, 2 of Koplik's cases (983), an 8 year old and an 11 year old girl, Lewinberg's (2405) case, a 13 year old girl, and E Cecil Williams (2447) case, a 12 year old girl

Shortness of breath characterized 2 acute transient cases combined with marked tachycardia as mentioned earlier by Trousseau and Labarraque (58 and 94), a 14½

year old boy, and by Solbrig (249), an 8 year old boy In the first case, perhaps the rapidly enlarged pulsating thyroid may also have made breathing mechanically difficult (see §253 above) Batchelor's (2457) case of an 8 year old girl and Gagnon's (357 and 381) case of a 12 year old girl ended fatally.

In Lewinberg's aforementioned case severe dyspnoea accompanied a sudden transient exacerbation of the disease

§284. In milder cases of childhood Basedow's disease the general state of nutrition often suffers only slightly. Often, however, the muscular system is weak, and the fat layer underdeveloped. The child is frail and slight in appearance, the skin color pale or grayish or noticeably anemic. These cases were always severe and sometimes fatal. In Sutton's (418) very severe case, a 13 year old girl showed a high degree of emaciation and weakness, a paraplegia and bedsores. After a half a year of severe illness the disease took a turn for the better (see §258 above).

§285. In more than half of the cases no data are furnished on mental condition, emotional state, and nervous irritability. We can hardly err if we assume that most of these cases showed no important departure from normal. Nervousness is mentioned in 16 cases. In the very severe case of Murrel (474) it was mentioned expressly that the 14 year old girl, in spite of her regrettable condition, was quiet and did not wail or complain. Restlessness and irritability expressed in outbreaks of anger or fits of weeping was observed in 27 cases. In several instances a labile mood was emphasized One case showed compulsion fixations (Kronthal, see below).

In the majority of these cases the children were healthy at the onset and showed nothing noticeable in the personality Twelve cases had a hereditary nervous predisposition.

In 8 cases either the mother or both parents were nervous In Baginsky's cases (140) the father of the 12 year old girl patient was a heavy drinker In Zuber's (2036) case the father and the maternal grandfather were addicted to alcohol. Ovazza (2217) reported that the father of 3 children with Basedow's disease was an alcoholic In the cases of Kronthal (1124), Mathes (2511) and Homén (1043) the mother also suffered from typical Basedow's disease In the first of these cases the 12 year old daughter had Basedow's disease with conspicuous nervous signs, unstable moods, attacks of weeping, and compulsive ideas (see §156 above) In Mathes' case a palpable goiter was absent This 10 year old girl had an otherwise typical disease picture. In the cases of two children whose mother had Basedow's disease, a 10 year old girl and a 15 year old girl, Homén found tachycardia, a small soft goiter and slight tremor

A 10 year old girl had an incomplete form of Basedow's disease There was no goiter (Lewinberg 2405) The mother had a soft goiter comprising the whole thyroid gland. This had begun in her eleventh year and continued to grow slowly until puberty. Since that time she suffered at times from palpitation and hot flushes She had become nervous and the smallest difficulty caused her to tremble During the examination the pulse fluctuated between 76 and 100 One of her two children, a 12 year old boy, was very nervous and inclined to weep He often complained of

headache and dizziness. His sleep was uneasy The thyroid gland was somewhat enlarged. The pulse rate was 88 beats per minute There was a slight tremor of the lids when the eyes were closed The 11 year old daughter showed a slight enlargement of the isthmus of the thyroid gland She had a pulse rate of 100 to 104, slept poorly, often suffered from headaches At times she stuttered badly. J Holmgren's (3128) statistics include an account of a 12 year old girl with moderately large symmetrical goiter, tachycardia, and slight tremor Her mother had a deep goiter, palpitation, tachycardia, and tremor of the fingers

In addition to the above cases, a few more have been known in which the signs of Basedow's disease or of thyrotoxic goiter heart have been observed among several children of one family. In these cases the parents were healthy and no hereditary predisposition was known otherwise

R Daniel Brewer (1699) reported that 4 of 6 children of healthy, but poor parents who lived on a vegetarian diet, were attacked by Basedow's disease Exophthalmia was present in only 1 case All had tachycardia, thyroid enlargement, tremor, dermographia, and an increased sweat secretion Sugar was found in the urine in 2 instances

Beyard Holmes (1734) reported a family in which all 5 children showed thyrotoxic signs in more or less conspicuous form The oldest was a boy of 12, the other a girl of 2 Neither had exophthalmia The girl had tachycardia and tachypnoea A Lockhart Gillespie (1723), at an English institute for the deaf, observed 2 sisters who had

[illegible]
well developed, became timid and anxious for no obvious reason A short time later *a rapidly increasing swelling on the throat was noticed A rather large goiter was* found, also a pulse rate of over 100 beats per minute, a forceful heart action, moderate exophthalmia, a wide gape of the palpebral fissure, and a tremor of the arms and the tongue, but no emaciation In the case of his 5 year old brother who up to that time had developed well, a swelling appeared on the throat, became somewhat smaller and *grew once more There was pulsating goiter, the largest circumference of which* was 28.5 cm, a forceful cardiac apex beat and a pulse of 92 In the case of the 11 year old sister, the throat had recently swollen considerably Its greatest circumference was 37 cm At every heart beat vibration of the whole cardiac area was evident The pulse rate was 90 per minute

Lewinberg (2405) reported the histories of 3 sisters who suffered from a mild form of Basedow's disease In the case of the oldest, a 14 year old girl, the symptom complex was typical The 13 year old sister had no exophthalmia but an attack of shortness of breath, mentioned above The youngest, a 10 year old girl, had no goiter But otherwise the disease was typical

A 10 year old girl with Basedow's disease, as described by Nicoll (3165), came from a nervous family The father had tremor and exophthalmia An older brother had tachycardia and exophthalmia

In 7 cases, rapidly developing signs of Basedow's disease followed intense emotional disturbance. Nervous manifestations were conspicuous in the disease picture of these cases.

A 12 year old girl with a typical Basedow's disease, observed by Baginsky (1401 and 2144), was extremely frightened by the mistreatment to which an intemperate father subjected her and her mother A 12 year old girl, previously healthy and without hereditary predisposition, was described by R. Hirsch (3135). Palpitation, restlessness, anxiety and sleeplessness followed a visit to the morgue Directly afterward her mother noticed her eyes protruding from her head, and a swelling which had developed on the throat Furthermore, there was tachycardia, widening of the cardiac dullness on both sides, tremor of the fingers, and perceptible emaciation The illness dragged along for several months without much improvement Then the subjective condition and the nutritive state became satisfactory, although the objective diagnosis remained unaltered

Mathes reports (2541) 2 cases which belong here A 10 year old girl whose mother also suffered from Basedow's disease (see above) was frightened by some terrified horses She developed tremor of hands and legs, unrest, anxiety, sleeplessness, headache, and palpitation While the goiter could not be felt, there was exophthalmia, and all of the lid signs were present A 9 year old girl with hereditary predisposition (insanity in the family) had a fright when she fell from a wagon This was followed by tremor of hands and feet, choreiform movements of the whole body, palpitation, and anxiety She became excited, irritable, and unable to sleep A small goiter and strong exophthalmia as well as equivocal lid signs were found

A 9 year old boy (Lewin 777) developed tremor, after a violent shock. The speech became stammering in character From then on the symptom complex of Basedow's disease developed gradually

A 14 year old girl reported by J Holmgren (3138) had a shock when a cyclone passed over her home She became anxious and excited At first it seemed as if she was "not all there" Then came a sensation of choking and shortness of breath There was a small, soft, quite symmetrical goiter The pulse rate was 120 per minute Distinct fine tremor of the hands was noticed Exophthalmia was not present The mother was also very nervous

In Solbrig's (249) case, mentioned several times, the excitement over the award of a prize was presumed to be the cause of a rapidly progressing Basedow's disease (see §253 above)

§286. The occurrence of typical chorea or slight choreiform movements is relatively frequent in Basedow's disease during childhood; 10 cases of this sort are known so far. In 2 cases observed by Gagnon (357 and 381), an 8 year old girl and a 12 year old girl, the illness was severe.

In the first case, death occurred after a 5 year long illness characterized by emaciation and weakness The other case showed tachycardia of up to 150 beats per minute, marked exophthalmia, shortness of breath, weakness, and emaciation Later came attacks of asphyxia. Chorea disappeared after 2½ months When discharged, the child was so ill that she was expected to die

Among 4 children with Basedow's disease observed by Jacobi (336), a 13 year old girl had a violent continuous chorea except during sleep The mother was anemic and nervous, and the girl had always been frail It was reported that she had once fallen on her head and that she had suffered for several years from Basedow's disease complicated by a transient right hemiplegia

A case reported by Bouchut (280) was that of a 13 year old girl from a goiter region, but without known hereditary nervous predisposition She had typical Basedow's

disease, complicated by fainting spells with cyanosis and periodic paralysis of the limbs. The atta[illegible]
20 times within [illegible]
Occasionally, h[illegible]
four extremities after cessation of these attacks Five months later the child enjoyed the best of well-being subjectively, only the goiter had not changed and slight exophthalmia still remained

In the case of a 9 year old girl described by v Mathes (2541) tremor and choreiform movements of the whole body followed a shock Then the complete symptom complex of Basedow's disease developed (see above)

Steiner (1513) observed slight chorea in 2 cases, in the course of Basedow's disease *In the case of a 9 year old girl it was fully developed, in the case of a 12 year old girl* eye signs were absent Both cases showed nervous and mental symptoms, irritability, outbursts of anger, emotional instability, anxiety, and forgetfulness A small and slight 15 year old girl was reported by Chr Ulrich (2028) Choreiform movements were among the signs of Basedow's disease together with a slight enlargement of the thyroid gland and tachycardia In addition mental sluggishness, weakness, slowness of speech, dryness of the skin, and exfoliation of the face were evident (see §221 above)

A 10 year old pale, thin, girl, whose case history is reported by Lewinburg (2405), had distinct choreiform movements of the head and of both thumbs recognizable by careful observation A palpable goiter was absent, and the Basedow's disease during the whole period of study was mild Two sisters also suffered from Basedow's disease (see above)

In the case of a 13 year old girl, observed by Zuber (2036), Basedow's disease began acutely following the use of iodine It ended in a cure six weeks later Choreiform movements occurred during a concurrent severe rheumatism of the joints with pericarditis (cf §253 above)

As can be seen from the above survey, all of these cases were female patients from 8 to 15 years of age Half of all of those affected were between 12 and 13.

For the sake of completeness we mention one more case reported by Bootz (694), a boy *with no hereditary nervous predisposition At the age of 5 he had chorea minor*, and in his twelfth year dyspnea, palpitation, hot flushes, sweating, and enlargement of an existing small goiter Besides the above symptoms, a pulse rate of 100/minute, a forceful cardiac apex beat, definite cardiac dilatation, moderate *exophthalmia, v Graefe's sign and dermographia were evident (see also §116)*

§287. A complication with epilepsy was observed in 1 case by Oliver (783).

An 8 year old girl had mild, and later severe epileptic attacks When she was 14, the signs of Basedow's disease appeared

Among other cerebral complications in addition to the aforementioned peculiar fainting attacks in Bouchut's case and a transitory rightsided hemiplegia in Jacob's case (see above) there was almost complete para-

plegia in Sutton's (418) case of a 13 year old girl. Following improvement in the Basedow's disease the paralysis also disappeared. Steiner (1513) incorrectly regarded this as an hysterical sign. An 8 year old girl, observed by Hock (1323), had a large, vascular goiter, palpitation, a pulse rate of 142 and a tremor of the extremities Paresis of the left rectus muscle occurred as a complication.

According to Steiner's view (1513), over half of the children with Basedow's disease show signs of hysteria. That is certainly enormously exaggerated, and is based on an error in the interpretation of the symptoms On the contrary, the complications with hysteria seem to be rather rare in childhood. In the case of a 12 year old girl, whom Steiner himself had studied, definite signs of hysteria were evident. Besides irritability, anxiety, emotional instability, and forgetfulness, anaesthetic zones on the back could be demonstrated and there was an area of hyperasthesia in the lumbar region

§288. Vasomotor disturbances have often been observed in children with Basedow's disease. Sometimes the children complain of hot flushes or of a hot head. In the case of a 15 year old girl J. Holmgren (3138) found an erythema in the form of large spots on head and neck. Variot and Roy (2132) observed a 4½ year old boy who had become emaciated following whooping cough. Trivial episodes, such as the insertion of a thermometer in the rectum brought forth a sudden scarlatiniform flush spreading over the whole skin. In the case of a 12 year old girl Chvostek (333) observed an intense reddening of the face especially behind the ears, first on one side, then on the other, sometimes on both. This occurred without evident cause, and lasted several minutes. Demme (400) observed a 3½ year old child who had outbreaks of perspiration on the right side of the face, reddening of the external ear, and a temperature rise in the right external ear canal of half a degree above that of the left one. Lewinberg (2405) reported dermographia in the cases of two sisters with Basedow's disease, aged 13 and 12. Bootz (694) similarly reported the case of 14 year old boy.

§289. Increased sweat secretion occurred in the cases of Variot and Roy (2132), a 4½ year old boy, of Uphoff (2131), a 6¾ year old girl, of Bootz (694), a 14 year old boy, and of Stegmann (2764), a 14 year old girl. The previously mentioned 3½ year old child observed by Demme (400) had outbreaks of sweating on the right side of the face only.

§290. Although children are readily inclined to show a rise in body temperature, we find hyperthermia noted in only a few cases of Basedow's disease. In a few cases, normal body temperature is mentioned specifically.

In the 2 fatal cases of Schwekendiek (569) and Ditisheim (1293) it was emphasized that the temperature was normal.

Some of those cases in which it was temporarily elevated were mild or incomplete forms of the disease, as that described by *Ehrlich (888)*, an 11 year old girl, by Fr. Kraus (984 and 1871), a 13 year old girl whose body temperature rose at times to 40°, and the peculiar case briefly described above by A S. Smith (680).

In a case described by R Förster (893) the disease began with a rise in temperature A 10 year old boy without hereditary predisposition had an obstinate diarrhea accompanied by a rise in temperature This hyperpyrexia continued after cessation of the diarrhea and disappeared only after tachycardia of 124 beats per minute and dilatation of the heart had occurred Improvement soon followed Exacerbation of the disease about a month later was again initiated by a rise in temperature Other signs at that time included a slight exophthalmia, and a moderate pulsating enlargement of the thyroid gland The boy became emaciated and very pale Finally, there was lasting improvement following the use of Fowler's solution, 2 or 3 drops twice a day After this medication had been administered for about eight weeks a brown color spread over the whole body, color was noticeable especially on the upper thorax When the arsenic was discontinued seven weeks later, the color gradually began to fade After three years only light pigmentation was found on the chest and abdomen There was slight protrusion of the eyes, slight swelling on the throat, and somewhat widened cardiac dullness

§291. Except for this skin pigmentation which the observer believed to be due to the prolonged use of arsenic, no pigmentation has been noted in Basedow's disease during childhood Depigmentation in the form of white spots (vitiligo) has been observed among children in 2 cases. One case was the 12 year old patient of Baginsky (1401 and 2144) mentioned above Relatively large white spots were scattered over the otherwise tender but brownish skin. These disappeared completely following an improvement in the disease. A 13 year old girl, reported by Lewinberg (2405) had a large number of white spots about the size of lentils distributed symmetrically on the dorsal surface of both forearms and hands.

Loss of hair was observed by Kronthal (1124) in the case of a 12 year old girl mentioned above. Ridges on the fingernails were described by Uphoff (2131) in the case of a 6½ year old girl with nervous parents. Facial atrophy on one side, and an unequal development of the two mammae was observed by Baginsky (2144) in the case of a 13 year old girl.

§292. A 12 year old boy came under Stephensen's (2584) treatment because of a recurrence of angioneurotic edema of the upper eyelids. Four months later, unmistakable signs of Basedow's disease appeared, including moderate enlargement of the thyroid gland, tachycardia of 120 beats per

minute, and slight exophthalmia. Tremor, emaciation, nervous symptoms and lid signs were lacking

Swelling of the face and edema of the lower extremities not to be interpreted as cardiac edema, were described by K. Ehrlich (888) in the case of an 11 year old girl who, like her older sister, had had a goiter for a long time. For two years she suffered from palpitation and mental excitability. Landstrom and Ahlberg (J Holmgren 3138, p. 99) observed swelling of the face in the case of a 6 year old girl with definite Basedow's disease.

Edema of the lower extremities, chest, abdominal wall, and eyelids was also noted in the severe, fatal case of a 13 year old boy reported by Ditisheim (1293) The edema increased during the final days and then was associated with ascites Besides other changes (see below) a fatty degeneration of the left ventricle and thrombosis of both *venae iliacae* and *femorales* occurred.

A 10 year old child observed by F. E Batten (2458) had swelling and pallor of the face attributable to a complication with myxedema (see §221 above). The child had a waddling gait, a squeaky voice, and a slow, dull personality. These were accompanied by considerable enlargement of the thyroid, forceful heart action, and tachycardia up to 180 beats per minute. Spencer Watson (639) was struck by the slowness of speech and mental dullness combined with the chief signs of Basedow's disease in the case of a little girl who previously had not shown these traits. Ulrich's (2028) similar observation of a 15 year old delicately built girl we have already considered (see above)

A 6 year old Italian boy, a 15 year old Italian girl, and a 14 year old girl of English descent were observed by Baldwin (1265) Each had Basedow's disease complicated by the disease picture of myxedema (see §221 above).

§293. The experiment described by Fr. Kraus and H. Ludwig (984), concerning occurrence of increased glycosuria in the case of a 13 year old girl with Basedow's disease, seems to have been the only one made on a child with this disease This is the more to be regretted because an unusual reduction in the tolerance for fructose was discovered in the case of this particular girl. The value was lower than any ever found among adults (see §230 above). In the cases of 2 among 4 children with Basedow's disease, Brewer (1699) found sugar in the urine *Diabetes mellitus*, however, has never been encountered among children with Basedow's disease. Stridsberg[1] reported cyclic albumenuria in the case of a 9 year old girl with a mild case of Basedow's disease The volume of urine is called abundant in a number of cases. In only one case at the most can one speak of a polyuria,

[1] Studier ofver den s k cykliska albuminurien Akademiska Abhandelinger Stockholm, 1903.

that of Ditisheim's 14 year old boy with a mild case of Basedow's disease (1293). The daily volume of urine varied between 2300 and 3500 cc

§294. We have emphasized before that the great majority of Basedow's disease cases in childhood were rather mild and associated with relatively few signs (see §277 above). *In about a third of all the cases known to me,* the disease took the form of thyrotoxic goiter heart, and, during the course of the observation, did not assume the complete pattern of Basedow's disease. We have seen above that the disease can appear in several members of the same family, first, in one form and then in another (see §285)

The course of the disease in childhood is usually slow and its development quite gradual We have already cited the few cases with acute onset and a course of only a few weeks (see §252 above) Two of these were very severe and ended fatally (1 case of Schwekendiek, 569, a 2½ year old boy, and 1 of Ditisheim 1293, a 13 year old boy) Complete recovery of the other cases, notwithstanding occasional very turbulent manifestations, followed in the course of 2 to 10 weeks In the peculiar case observed by A S Smith (680), described briefly above (§279), use of quinine for 10 days resulted in disappearance of the thyroid enlargement and the other signs of the disease

In a number of cases the symptom complex developed rather quickly although the further course was chronic *This was characteristic in most* of those above-mentioned cases where the disease broke out following a mental trauma (see §285) In a few other cases the disease took only a few weeks for complete development Unfortunately we miss in many case histories statements about the onset of the illness More than half of all of *the reports* on Basedow's disease in childhood lack all information concerning the outcome of the disease Many of these children were under observation for only a short time

§295. In about half of all of the cases which furnish sufficient data concerning *the course of the disease, the duration of the disease was not as long* as that usually found in adults In these cases it varied between two weeks and three years.

We have just spoken of acute cases with rapid course After a duration of a few months a cure or improvement was achieved in the cases of Variot and Roy (2132), a 4½ year old boy, of Walitzki (2134), a 5 year old boy, of Hawkes (102), a 5½ year old girl, of Jacobi (336), two girls, one 9 and one 10 years old, of Hingston Fox (1196), a 12 year old girl, of v Dusch (403), a 13 year old boy, of Bouchut (280), a 13 year old girl, of J Holmgren (3138), a 12 year old girl (In the last-mentioned case an obstinate relapse occurred The course of the disease extended over the rather long period of 1½ to 3 years) Other cases Bootz (1694), a 14 year old boy, Ch G Kerley (1596), a 13 year old girl, Ditisheim (1293), a 14 year old boy, Baldwin (1265), a 15 year old girl, R Forster (893), a 10 year old boy, Uphoff (2131), a 7 year old girl, and

finally Sutton's very serious but favorably ending case (418), a 13 year old girl (see §258 above) There has also been a cure effected relatively quickly in those cases in which surgical interference took place and in 1 case treated by X-ray (see §296 below) In the other cases concerning which something could be learned about the duration of the disease, the cure took over three years.

§296. In general, it can be said that in children the tendency toward cure or extensive improvement is greater than in adults. Nevertheless, a real and lasting cure is also rather rare. How cautious one must be in this regard we have emphasized above repeatedly. The correctness of this warning is shown especially by Baginsky's case (1401 and 2144). A 12 year old girl seemed to have recovered completely from definite Basedow's disease after a relatively short treatment. Even the vitiligo spots scattered over the whole skin had disappeared entirely (see §281 above). Seven years later an obstinate relapse occurred which did not yield to treatment. The child was withdrawn from further observation

Of 62 usable cases, 19 were reported cured, that is 30 64% (Baginsky's case is not counted here) Among these are 6 cases mentioned several times which progressed rapidly after the sudden development of the symptom complex and ended in a complete cure after a few weeks (§253) In a few cases with a chronic course, a reduction of the goiter and gradual disappearance of the other symptoms was brought about by medication and dietary measures, Hawkes (102), a 5½ year old girl, Romberg and Henock (39) and Bootz (694), a 14 year old boy. Stegmann (2764) achieved a cure in the case of a 14 year old girl by means of X-rays. In Weidemann's (685) case of a 14 year old girl, partial removal of the goiter brought about a cure. In the case of a 14 year old girl with the symptoms of goiter heart observed by myself, and in Landstrom's (2849) case, the cure was accomplished by ligation of both of the upper thyroid arteries and the right lower one. In another case operated on by Landstrom, a 6 year old girl (J Holmgren 3138, p. 99), a cure likewise seems to have resulted In the case of a 14 year old boy the complete symptom complex of Basedow's disease had been fully developed since his eleventh year. Haim (2831b) tied off the *carotis externa* near the origin of the *art thyroidea super*, preliminary to an operation on the upper jaw for a fibrosarcoma arising from the pulp of a wisdom tooth which had not yet broken through. After the operation, the signs of Basedow's disease disappeared entirely. Heart action became normal again. Neck circumference was reduced by more than 3 cm Exophthalmia disappeared. In 3 of the cases observed by Baldwin (1265), the Basedow's disease was cured but then the symptoms of myxedema developed (see §292 and §221 above).

Twenty-one cases, or 33 87%, were greatly improved. Among these were very severe illnesses like those observed by Sutton (413) in the case of a 13 year old girl for whom a fatal outcome had been feared (see §258 above) and by G. Wolf of an 11 year old girl (2895).

More or less improvement was achieved in the less severe but very typical cases of Demme (400), a 3½ year old girl, of Variot and P. Roy (2130), a 4½ year old boy, of Wahtzki (2134), a 5 year old boy, of Jacobi (336), a 10 year old girl, of R Forster (893), a 10 year old boy, of Hingston Fox (1196), a 12 year old boy, of Bouchut (280), a 13 year old girl, of Kalm (627), a 13 year old girl, of Ch Gilmore Kealey (1596), a 13 year old girl, and of Ditisheim (1293), a 14 year old boy

Distinctly developed but rather mild were Koplik's (983) two cases, an 8 year old girl and an 11 year old girl, and Jacobi's (336) case, a 13 year old girl. All of these cases improved with suitable treatment.

Whether the cure or essential improvement of all of these cases continued has become somewhat dubious in view of Baginsky's observation. On the other hand, many of the children discharged as cured would probably have been classified as such even after a physical examination at a later date

Definite improvement in the general condition and in the subjective state occurred without a notable change in the objective signs in 2 cases of typical Basedow's disease, a 4½ year old girl observed by Scharkin (3043) and a 12 year old girl reported by Rahel Hirsch (3135)

There were 12 cases (19 35%) which were only slightly improved, among them 3 with the signs of goiter heart Two remained unchanged at the close of the observation

Six children died of Basedow's disease The deaths comprised, thus, 9 68% of all the cases in which data on the outcome were available However, certainly only a small fraction of the 70 cases which had no notation about their outcome ended fatally. The death rate from Basedow's disease during childhood must be relatively low, surely not higher than 4.5%.

Compared with the mortality from Basedow's disease in general (see §257 above) the danger of a fatal outcome seems definitely less during childhood

The 6 cases which are known were all very severe It is worthwhile to take these in some greater detail.

Schwekendiek's case (569) was a 2½ year old boy who, in the first thirty months of his life, appeared to be in blooming health The first sign of illness was a slight protrusion of the eyes observed by his mother At the same time he lost his appetite Six weeks later the child, already very feeble, developed a whooping cough lasting almost two months The pulse was weak and thready at 160 beats per minute The cardiac apex impulse had become forceful from the beginning of the illness A definite enlargement of the thyroid gland could not be demonstrated There were only a few enlarged tortuous blood vessels over it The child became restless and irritable and cried a great deal During the further progress of the disease, exophthalmia advanced

signs of congestion, death ensued As emphasized previously (see §290 above) body temperature had remained normal throughout this illness.

A case observed by Batchelor (2451) was that of a 3 year old girl with no hereditary predisposition She had enjoyed the best of health before she contracted whooping cough Three or four months later a protrusion of both eyes was noticed The child had bursts of anger which she had never showed before This girl was sent to the seashore When she returned 3 months later there were marked exophthalmia, v Graefe's sign, definite enlargement of the thyroid, especially of the right lobe, tachycardia of 120 beats per minute, and rapid carotid pulsation

A few months later the little patient was attacked by influenza and pneumonia and within a few days her status was very critical In the further course, exophthalmia increased still further, but fluctuated somewhat in prominence from time to time The lids could not be closed in sleep At the slightest movement the child became almost breathless Then came attacks of diarrhea and vomiting, and three and one half years after the onset of the first symptom, the girl died of exhaustion

Gagnon's 2 cases (357 and 381) have already been mentioned They were an 8 year old girl and a 12 year old girl who had the disease, complicated by chorea

A 14 year old girl, observed by Murrell (474), had tachycardia of 130 beats per minute, considerable enlargement of the heart, a symmetrical enlargement of the thyroid gland, and conspicuous protrusion of both eyes In the further course attacks of obstinate diarrhea ensued Soon afterward the girl died of exhaustion after she had been under observation for a year (see also §285 above)

In the case of a 13 year old boy, reported by Ditisheim (1293), a complication by hereditary lues was not expressly emphasized in the case history This patient was the ninth among ten children There had been three premature births; three children died at birth or during their first year, three others remaining alive were sickly The patient himself had always been healthy, well-developed and cheerful up to the

general condition became steadily worse There was a small, threadlike pulse of 164 beats per minute, a goiter occupying the entire thyroid gland, moderate exophthalmia, and edema of the eyelids, the lower extremities and the wall of the chest Cheeks, lips and nose appeared cyanotic The abdomen was distended, with noticeable fluctuations in size The liver was enlarged Progress in the edema and heart failure preceded death after ten weeks of illness The autopsy, the only one among the fatal cases in children, showed changes partly attributable to congenital syphilis There was a large goiter, partial adhesion between pericardium and heart, blood in the pericardium, a high degree of fatty degeneration of the left ventricle, hydrothorax, embolic conges-

- - -
and *femorales*

§297. For obvious reasons, the first signs to be noticed in Basedow's disease during childhood are, as a rule, not the cardiovascular symptoms, but others which are distinguishable by observation In about half of all of the cases in which acceptable data concerning the sequence of the symptoms are available, the enlargement of the throat was the change first attracting attention. In several of these cases there was also, almost simultaneously,

complaint of rapid palpitation or unusual fatigue, decrease in appetite, poor sleep, or nervous unrest.

This was the case in the observations of Hawkes (102), on a 5½ year old frail and nervous girl; of Bouchut (280), a 13 year old girl, of Fr Krause (984 and 1871), a 13 year old girl; of Dittscheim, a 13 year old boy and a 14 year old boy, and of Landstrom (2849), on a 13 year old girl

In a case reported by Wolfe (2895) of an 11 year old girl, the swelling in the throat and the protrusion of the eyes were discovered at about the same time. Soon afterward the other signs also appeared In the severe case observed by Sutton (418) of a 13 year old girl, protrusion of the eyes came soon after a visible swelling of the thyroid gland became evident In the case of a 14½ year old boy under observation by Trousseau (94) the enlargement of the thyroid gland progressed to an ominous degree within a few days, and the Basedow's disease signs progressed acutely to full development. Just as rapidly as they had arisen, these threatening signs disappeared again (see §253 above). The illness of a 13 year old girl, observed by Ch Gilmore Kerley, began with painful swelling of the right side of the throat, said to have followed a cold In the course of two months the symptom complex of a very severe Basedow's disease developed.

Attention has already been directed (§279) to the cases reported by A S Smith (680), illustrating periodic enlargement of the thyroid gland with Basedow's disease signs in the case of an 11 year old boy.

In a case observed by Zuber (2035), a 13 year old girl had had a swelling on the neck for several months which had caused no trouble at all. After administration of iodine the Basedow syndrome appeared rapidly This disappeared again quickly following discontinuance of the medication (see §253 above).

A 14 year old girl treated by Stegmann (2764) had had a small goiter since she was 4 years old, this gradually increased in size Palpitation began when the patient began to use thyroid tablets Although the medication was discontinued, the condition improved for a short time only Soon afterward the whole symptom complex of Basedow's disease appeared in acute form. After repeated X-ray treatments it disappeared completely within a month (see §253 above)

A 5 year old boy reported by Orzza (2217) had had a small goiter at the age of 3 After two months it had disappeared again Later, a new growth occurred in the form of a pulsating goiter At the same time palpitation and tachycardia occurred A swelling of the throat of the 11 year old sister had been noticed only two weeks before the examination This was accompanied by a tachycardia and marked pulsation of the chest wall with every heart beat (see §285 above)

In the cases of Uphoff (2131), a 7 year old girl, of Kocher (2131), an 8

year old boy, of Weidmann (685) and Bootz (694), a 17 year old girl, and in the case of a 15 year old girl studied by myself a swelling on the throat had been present for a long time. Accompanying a rapid growth of the goiter prior to the examination, the Basedow's disease signs developed either gradually or precipitously. A preceding enlargement of the neck for 1½ to 3 years was noted in the cases of Hock (1323), an 8 year old girl; of Uphoff (2131), a 6½ year old girl and a 12 year old girl; and of Lewinberg (2405), an 11 year old girl. In the case of an 11 year old girl observed by Ehrlich (888) and in the case of an older sister, a rather large swelling on the throat was said to have been noticeable soon after birth. Tachycardia, palpitation and secondary symptoms appeared in her ninth year only.

Protrusion of the eyes appeared as the first sign of the disease in the cases of Schwekendiek (569) and Batchelor (2457) (see §296 above); of Demme (964), a 5 year old boy (see §253 above); of Lawson (2403), a 12 year old girl; and of Lewinberg (2405), a 10 year old girl and a 14 year old girl. A palpable goiter did not develop at all in the case of the 2½ year old boy observed by Schwekendiek, and in the case of a 10 year old girl reported by Lewinberg. In Demme's acute case the goiter became distinct only two days after the onset In the other cases its appearance was noticed three to six months after protrusion of the eyes.

In the case of a 13 year old boy observed by v. Dusch (403) the illness began with palpitation. A 12 year old girl treated by Kronthal (1124) had complained of palpitation for over a year. Then the protrusion of the eyes was noticed, and soon afterward the other signs developed. A 12 year old girl observed by Steiner (1513) had suffered from palpitation since her sixth year In Hingston Fox's (1196) case of a 12 year old boy, palpitation had been present for a long time, a year before the examination tremor of the hands was observed. Four months later there was a protrusion of the eyes. In the cases of Chvostek (333), a 13 year old girl, and of Jacobi (3336), a 10 year old girl, fatigue, weakness and palpitation were the first noticeable disturbances.

In the case of a 5 year old girl observed by Wahtzki (2134) the disease began with loss of appetite and emaciation. Then, in rapid succession, the complete symptom complex appeared. In Variot and Pierre Roy's case (2132) weakness and emaciation were the consequence of a whooping cough with bronchial pneumonia one and one half years before. One year after a nervous cough, exophthalmia, tachycardia, swelling of the throat, and several secondary signs of Basedow's disease appeared.

A 10 year old girl reported by Lewinberg (2405) had been noticeably nervous for a long time. Palpitation was followed by the other symptoms. A 7 year old boy, observed by Ovazza (2217), became timid for no obvious reason. Shortly afterward a swelling on the throat was observed (see §285

above). In the case of a 12½ year old girl treated by H. Muller (853), a certain awkwardness in the use of the hands was noticed first Two weeks later the symptom complex of acute Basedow's disease appeared (see §253 above).

In the cases of Baginsky, *Hirsch*, Mathes, *Lewin*, *Holmgren* and *Solbrig*, where Basedow's disease directly followed a violent shock or great nervous excitement (see §285 above), a sense of anxiety, unrest, sleeplessness, palpitation, or tremor were the first signs to appear.

The exceptional onset of the disease with a rise in temperature and obstinate diarrhea in the case of a 10 year old boy observed by Forster (893) has been noted (§290).

Distribution of Basedow's Disease

§298. Suitable data for a graphic picture of the geographic distribution of Basedow's disease are still scarce. Those we do have vary with respect to the pathological data from which they are derived. Nevertheless, a few generalizations can be made from what we do know In 1886, Hutchinson (664, p. 32) had already stated quite correctly that Basedow's disease "is precisely one of those maladies which we might have believed likely to be influenced by place of residence". All civilized countries have furnished reports on the occurrence of Basedow's disease But there are plainly some very great differences in respect to frequency and distribution

Within Germany and German-speaking regions, its distribution is very unequal In middle and northern Germany, Basedow's disease seems, at least in many regions, more frequent than in southern Germany Eulenburg claimed that he had seen it more often on the Baltic coast than in Berlin Among the numerous patients in my polyclinic group there is approximately one case of Basedow's disease among every 1000 patients From statistics collected by Passler (1362) from the polyclinic in Jena it appears that Basedow's disease occurs very frequently in Thuringia Among 2800 patients, 58, or 2% of all the patients, showed signs of Basedow's disease V Mathes (1619) likewise had gained the impression that the disease seemed unusually frequent This is confirmed also by the relatively large number of Basedow's disease cases which comes to the Jena surgical clinic for operations (Riedel 1494, K Schultze 2750 and 2881a) In Hesse also Basedow's disease seems to be not infrequent Uphoff (2131) counted 46 Basedow's disease cases among 28000 patients who visited the Marburg Medical Clinic between the years of 1890 and 1900 That amounts to 0 16%. From Professor Friedrich it has been learned that the number of Basedow's disease goiter cases which come to the Marburg surgical clinic for operation, is relatively large. It is noteworthy that in Frankfurt on Main also, Basedow's disease represents a substantial proportion of the operative cases

of Rehn (1901 and 2000). In Thuringia, and to a certain extent in Hesse, simple goiter cases also are much more frequent than in the northern regions of Germany

In a few badly afflicted goiter areas Basedow's disease in its typical form is, however, less frequently encountered than in the regions in which goiter occurs only sporadically.

H. Bircher (1407) in Aarau declared that Basedow's disease is rare in his practice in an endemic-goitre area [1]

Eugene Bircher (3215) stated that, among 400 goiters only 2 Basedow's disease goiters occurred, and these were only mild cases

Lebert found Basedow's disease more frequent in North Germany than in Switzerland Eichhorst (2820c) declared, on the contrary, that if he included his experience in private practice he had seen "far more" cases of Basedow's disease in Zurich than in the various parts of North Germany. Among the patients of his clinic, cases of Basedow's disease occur not infrequently. Among 35,475 patients treated in the Zurich Medical clinic from 1884 to 1906 there were 40 cases of Basedow's disease or 0.1%. This is the more striking since a helpful report from my colleague O Haab indicates that Basedow's disease cases are very seldom seen in the Zurich eye clinic The incidence was estimated as 1 among every 10,000 patients. On the other hand, goiters of moderate size occur very frequently in the Zurich region Very sizeable goiters, some of them substernal, are not rare.

Fr Kraus (1871 and 2090) emphasized the relative infrequency of definite Basedow's disease cases in Styria and in Carinthia. W. Scholz (3187) has declared that the Graz ambulatory clinic rarely has a typical case of Basedow's disease, hardly one a year Cases of goiter heart, on the other hand, are relatively frequent It is peculiar that many goiter patients develop Basedow's disease only after leaving the goitre area.

Wilms'[2] experiments on production of goiter in rats by drinking water of a goiter region have established that the toxic action of the water is not increased by filtration but apparently by heating over 70° Wilms supposes that toxins present in the water counteract the poisons acting in Basedow's disease as a result of the increased function of the thyroid gland

Broers (2810) had found that enlargement of the thyroid gland occurred more frequently in the city of Utrecht than in the parishes of the province of the same name, but that a frequent occurrence of Basedow's disease symptoms was not demonstrable by any means.

Savage (1147) emphasized that, among 1000 cases of goiter assembled in

[1] 22 to 50% of the school children and 15 to 30% of the recruits in the parishes on the right bank of the Aar river have goiter

[2] Experimentelle Erzeugung und Ursachen des Kropfes, Deutsche med Wochensch XXXVI, Nr 13 p. 604

Cumberland, he had not come across a single case of Basedow's disease. Exactly the opposite is stated by A. Maude (1133) Within 6 years, in a small country region in England of about 3,000 inhabitants, there were 55 cases of thyroid enlargement including 12 cases which showed more or less clearly developed signs of Basedow's disease.

Frank Billings (2806) was acquainted with several regions north of Central Illinois where a large number of simple goiter cases originate, and also more Basedow's disease cases than from other regions One small village in the state of Michigan had 8 cases of goiter and 2 cases of Basedow's disease.

A most unusual occurrence was observed by Hand (660)—a narrowly limited endemic incidence of goiter and of Basedow's disease In a State Reform School in St. Paul, Minnesota, with 140 inmates, 44 boys developed goiters In a neighboring school for girls only 1 among 19 pupils became ill The water and food were alike for all All were healthy and took physical exercise regularly In a certain number of cases enlargement of the thyroid was accompanied by tachycardia, palpitation, and exophthalmia Goiter does not occur endemically in this region, and no inmate came from a goiter region After two and one half months the epidemic disappeared Nothing was altered in their way of living aside from the use of Lugol's solution

Evidently much depends on the nature of the thyroid enlargement Very instructive in this regard is an observation made in Stuttgart by Hofmeister (2679). The goiters of patients who come from the Stuttgart Basin and from the valleys of Rems and Murr, northeast of Stuttgart, are "remarkably often" associated with signs of the so called goiter heart The goiters from the eastern portion of the Black Forest, on the other hand, show these signs "very rarely". Goiters with thyrotoxic heart disorders are parenchymatous goiters. They are filled with blood, of homogenous composition, and without macroscopically recognizable signs of degeneration The others showed signs of degeneration, cyst formation, calcification etc

In certain sections of the Austrian Alps goiter is endemic Not infrequently, it is accompanied by cretinism. Yet the large, disfiguring, colloid and cyst goiters occur more rarely. On the other hand, moderate, rather symmetrical, soft elastic swellings of the thyroid gland, which produce a *prominent rounding out at the front of the throat and are called puffed-up* neck, are very frequent Also, Basedow's disease in its typical form as well as in its mild or incomplete stages is rather widely distributed there[1]

J Holmgren, physician-in-chief of the department of internal medicine of the provincial hospital at Falun, Sweden, very kindly informed me, in reply to my inquiry, that in Dalarne, the only province of Sweden in which

[1] In 1909 v Eiselsberg mentioned that he had removed 756 goiters in his private practice and in his clinic since 1901 Many of his goiter patients must, of course, have come from various parts of the monarchy

goiter occurs endemically, typical Basedow's cases are not rare, and that goiter patients with thyrotoxic complications, tachycardia, fine tremor, and other nervous signs come under observation "remarkably often", especially women from 30 to 40.

Among 1905 patients received in his department during the years 1906 to 1908 23 had Basedow's disease, 5 men and 18 women, or 1 26% If those with venereal and mental diseases are subtracted, the result is 1 35%. About half of these 23 Basedow's disease cases had a completely developed symptom complex If we consider that patients with incomplete Basedow's disease not requiring hospital treatment are not included in this figure, the percentage of Basedow's disease must probably be still higher.

In the Seraphim Hospital at Stockholm cases of Basedow's disease seem to come under observation not infrequently, as may be concluded from the reports of Landström (2849) and J. Holmgren (3138)

In Denmark, according to Gram's (1316) statement, Basedow's disease seems to occur rather seldom. Hardly 50 cases appeared in two of the larger hospitals at Copenhagen in the course of ten years. To be sure, Gram himself admits that Basedow's disease actually may have occurred more frequently, since its initial stages are often not recognized. Among 17 of his hospital cases, 12 were entered with other diagnoses.

In the Russian Baltic Provinces, especially in the region of the Gulf of Finland, Basedow's disease is widely distributed. Kroug (2700), whose case material was derived exclusively from regions on the Gulf of Finland between St Petersburg and Reval, estimated, on the basis of his collected data, the incidence of Basedow's disease to be about 3% of all of the patients

According to statistics published in Riga the frequency of Basedow's disease as stated by Kroug must reach the imposing figure of 13%. Kernig also, as he stated in the discussion following a lecture by Kroug, believes that in the area where he practices, which covers in general that of Kroug, the disease is quite common. Often, such patients are sent to the hospital with other diagnoses. v. Holst (2385) likewise confirms the wide distribution of Basedow's disease in this region, if its incomplete forms are included The Sokolow hospital reports 21 cases of Basedow's disease among 300 patients and 13 among 190 private patients, that is 7% in both categories combined

In England, Basedow's disease is widespread, especially in certain regions, and great interest in it has always been shown in this country

Murray (2213) gained the impression that it occurs much more frequently in the north than in the south. A relatively large proportion of H. Mackenzie's extensive material (2994), including over 212 cases, comes from certain parts of Kent, Surrey, Wiltshire, and from the Thames valley. In regions in which goiter is endemic, Basedow's disease is also more frequent. Burton

(7521) believed that the region around Cambridge is especially afflicted with Basedow's disease. He attributed this to the frequency of anemia and rheumatism in this region. The number of cases accessible to each observer is surprisingly large, for example: B. Bellingham (80), Russell Reynolds (932), A. Maude (1056 and 1133), Williamson (1523), H Mackenzie (2205 and 2994), and G. R. Murray (2553). The few available data from English and Scottish Hospitals give, to be sure, small percentages. Thus, S. West (686) counted only 3 Basedow's disease cases among 3179 patients in the ambulatory clinic of the Victoria Park Hospital in London According to A. Lockhart Gillespie (1723) 92 patients were treated in the medical division of the Edinburgh Hospital in the years from 1891 to 1896; that is 0 43% In the Middlesex hospital 19 patients with Basedow's disease appeared among 5941 patients treated between 1890 and 1895, making 0 27%.

But these data cannot serve as criterion for the determination of the distribution of Basedow's disease in England For West's figures are too low, and Gillespie's data refer only to patients under hospital treatment, thus omitting the mild and incomplete cases to a large extent

J Russell Reynolds (932) observed that during the four years in which he made his collection of cases, many more, and more severe, cases of Basedow's disease came under observation during 1888 than in other years He suggested an influence of the weather, since the year 1888 was especially cool and lacking in sunshine Atmospheric pressure seemed to have had no effect

A. Maude (1133) stated that the number of Basedow's disease cases received in St. Bartholomew's hospital had increased considerably since 1870 Rolleston (2226) also thought that Basedow's disease had become more frequent in recent years due to "the nervous strain of modern times".

In the United States of America Basedow's disease is widespread, at least in certain regions. Several authors report considerable numbers of cases observed by themselves, as for instance Dock (2641), W G. Thompson (2773), Frank Billings (2806), Ch. H Mayo (2411 and 2997), A Rufus Baker (2901), J. M. Jackson (2968) and others. Prof Friedrich (as he kindly wrote me) was struck on his journey in America by the large number of Basedow's disease cases, especially in the western states. Basedow's disease is very unevenly distributed in the United States, as shown by a report of J. Fr. Clarke (1832). Only 65 cases of Basedow's disease from 1892 and 1895 could be found by inquiry in the state of Iowa, which includes valleys of the great Mississippi and Missouri rivers. No doctor had more than 6 cases in his practice, and indeed one doctor had seen only 1 case during his practice of 45 years Would it be possible, perhaps, that some mild or incomplete cases were overlooked?

From France we have no data concerning the number of Basedow's dis-

ease cases in relation to the total number of patients in a polyclinic or hospital. Barrett (2044) has, as he states, the impression that Basedow's disease is more frequent in Germany than in France. From the foregoing collection of illustrative cases it seems that actually, except for the Paris hospitals, not as many cases come under observation in France as in Germany and England.

It is striking that among 15 patients with this illness at Korczynski's clinic in Cracow, as reported by Gluzinski, more than half were Jews, a group constituting only one-third of the population.

N V Sontag (1919) noted 50% of Jews among 82 cases with Basedow's disease treated in Neu Schmecks (Uj Tátrafured). In other areas a similar preponderance of Jews among such patients has not been evident. It may well be that entirely local conditions in that region are the determining factors

Drake Brockman, in Madras (649) declared, after he had reported a case of Basedow's disease involving a lady of English descent, that the illness is extremely rare among the natives, although great numbers of goiters occur in India. A Maude (1133) also mentioned that Basedow's disease occurred in India only rarely.

From Japan, only a few cases of Basedow's disease have come to our knowledge (*Otsuka 2557*) *According to an obliging communication from* the ophthalmologist Tatsuji Inouye in Tokyo Basedow's disease seems to occur in Japan more rarely than in Europe. No information is available as to *form and severity of the disease.*

According to Eshner (1715) Basedow's disease is rare among the Negroes in North America. He himself had seen only 2 cases, a 12 year old girl, and *a 35 year old man Denny (614) observed a Negro with a severe case of* Basedow's disease with fatal outcome. Sucker (2769) saw a 35 year old male Negro with a typical case of Basedow's disease with unusually high arterial tension.

§299. Th. Kocher (2966 p. 139) speaks of a *Basedow* constitution occurring in individuals, as well as in nations and races. It is based upon the histological structure of the thyroid gland, and represents in purest form what formerly was called a sanguine temperament. The active, excitable, always restless type of individual in whom the blood rushes to the face on the slightest occasion, the eyes shine more, sweat and tremor break out easily, and even small matters produce a strong emotional reaction, these have a special predisposition toward Basedow's disease.

According to Eichhorst's experience (707 and 2820c), delicately built, blonde, blue-eyed, as well as neurasthenic persons, and those who are chorotic and anemic, are easier prey to Basedow's disease. It is generally

accepted that anemia and chlorosis predispose to Basedow's disease, as Eichorst has pointed out. I refer in this connection to the material under §§226 and 228. Chlorotics do frequently exhibit signs of thyroidism. Seldom, however, do they have outspoken Basedow's disease (§228).

Furthermore it cannot be argued that most neurasthenia and hysteria is associated with a disposition toward Basedow's disease. It is true that the cases of Basedow's disease complicated by hysteria show the signs of this hysteria very soon after the onset of the Basedow's disorder. But despite the wide incidence of hysteria only a small fraction of the cases develop Basedow's disease.

The majority of patients with Basedow's disease in the clearly evident acute or chronic form were well up to the time of onset or at least showed very few signs of nervous illness. In other cases there was some excitability, increased irritability, or a personality change for a time before the onset of a clear cut Basedow's disease became apparent.

Among the 103 cases under my own observation there were only 9 whose detailed histories showed that since childhood they had been nervous, apprehensive, irritable, or easily fatigued. Three of the 9 had palpitations. In one instance the illness came 9 months after a marriage, in another it followed childbirth, and in the case of a male of 27 it came a year after a syphilitic infection. It is noted that a 47 year old patient suffered from a nervous illness for a long time before the outbreak of the Basedow's disease. A Basedow patient of age 21 had chorea at 13, and a female of 55 had attacks of obvious hysteria at frequent intervals from the time of onset of the Basedow's disease.

Stern's series (3060) of 81 cases includes 7 which he describes as the degenerative form of Basedow's disease (§245) with a history since childhood of nervousness, emotional instability, or tremors, and a family history of nervous disorders. These were among the 9 cases designated as Basedowoid. Eight had constant palpitations, usually associated with more or less obvious signs of nervous illness since childhood or for a long interval prior to the onset of the Basedow's disease. Th. Kocher's discussion is the only one in which a Basedow-disposition is mentioned. Persons with labile vasomotor nervous systems, the socalled "vasomotor individuals" (Kraus 2697) seem likely to develop Basedow's disease.

They are also the ones who acquire the symptoms of artificial thyroidism by incautious use of thyroid-gland preparations.

A facial expression showing little intelligence was noted in the cases of 2 girls who were small for their age, whose case histories were reported by Lewinberg. The mental sluggishness and dullness in the cases of Spencer Watson (639), Ulrich (2028), and Batten (2458) are to be considered as related to the edema (see §292 above).

My own material on Basedow's disease, which includes 6 girls not yet fully grown, does not reveal a definite type such as that delineated by Holmgren. By far the most frequent hair coloration in our region is light or dark brown, and the iris color is usually gray, gray-green, or gray-brown. Our

patients with Basedow's disease did not deviate noticeably from the predominant type.

The sketches in the preceding paragraphs on the geographical distribution of Basedow's disease, however incomplete the basic material may be, still seem to indicate that those areas where tall, blonde, and blue-eyed individuals live in larger numbers, have more cases of Basedow's disease in its developed or incomplete forms.

Furthermore, I believe that the various kinds of diet in the various nations and races are not without *influence on the distribution* of Basedow's disease

Basedow's Disease in Animals

§300. Although, in the opinion of experienced veterinarians, symptoms like those of Basedow's disease are often observed in dogs, and simple goiter occurs not infrequently in domestic animals in many regions, genuine Basedow's disease in animals is very rare A few reliably established cases have been *observed in dogs, cattle, and horses.*

The first of these was brought to light by Jewsejenko (744).

The left eye remained severely damaged by a corneal abscess

Sainton (2877) states that Cabot had seen all of the four main signs of Basedow's disease in a dog I have not been able to find any statement by Cabot himself concerning this matter

A 9 month old female dog (Seidenpinscher), retarded in its growth, was brought to Albrecht (1260) The bitch was very restless General discomfort, and lack of appetite were evident Her eyes protruded conspicuously, the palpebral fissure was unusually wide Raising and lowering of the head resulted in failure of the upper lid to follow the lowering line of vision The pulse rate was 130 beats per minute and the respiratory rate 30 to 35 per minute Heartbeat was pounding, pulse noticeably arhythmic, and carotid pulsations strong The goiter was quite large; the nutritional condition was poor Since therapy achieved no results, the dog was killed by chloroform A conspicuous anemia of the brain was found, but nothing noteworthy regarding the *sympathicus* The thyroid was greatly enlarged, and soft Close to it were three accessory thyroids Unfortunately, no histological examination seems to have been made

A fine typical case was observed by Lellmann (2201) in the case of a one year old male pointer dog In association with a poor state of nutrition there was also a goiter as large as a child's head, reaching almost to the breastbone, and of soft consistency. This goiter had pronounced *pulsation and distinct thrill. Pulse rate* was 130 beats

per minute, heart action was very forceful and cardiac dullness was increased Systolic whistling could be discerned Carotids pulsated very strongly Respiratory rate was 35 A pronounced bilateral exophthalmos completed the picture To this was added a slight nervous cough, periodic diarrhea, and vomiting Rather strong tremor of the whole body could easily be distinguished The dog was put to death with chloroform No autopsy was performed

A no less definite case was discovered by Sonnenberg (2761) in the case of a 13 year old male dog, a cross between a dachshund and a bracke This dog had been bitten in the neck two years before Following this injury a large swelling arose which gradually became smaller but did still not disappear entirely Three months later the swelling on the neck grew larger again and, for the final four weeks, had caused difficulty in breathing During this time the eyes had protruded and for the last two weeks the lids could not be closed The dog seemed to be moderately well nourished The hair was not glossy, the visible mucous membranes were pale, the pulse was 90 The cardiac apex beat was exaggerated, especially under the influence of excitement There was strong carotid pulsation Respiration was difficult and slow Appetite was poor There was a marked exophthalmos and a wide gape of the palpebral fissure The goiter extended into the chest It was of soft consistency On each side it took the form of a pear, the wider part downward Since the condition continued to deteriorate, the dog was put to death Unfortunately, the goiter was not examined histologically

Eggers (2820) also observed pronounced signs of Basedow's disease in a dog

Among horses, four cases of Basedow's disease are known.

The first comes from Jewsejenko (774) A thoroughbred English mare, after great exertion on the race course, had a sudden loss of appetite, violent cardiac palpitation, high pulse rate, strong pulsation of the carotids, accelerated breathing, considerable swelling of the thyroid gland, sleeplessness, edema of the eyelids, and, after 16 days, extreme exophthalmia with an inability to close the eyelids There was a whistling murmur at the base of the heart, a thready pulse and a temperature rise to 41° The animal died No autopsy was performed

Cadiot (1026), before the Society for Veterinary Medicine in Paris, reported a very well developed case involving a 15 year old horse The owner had bought it only six weeks before, and had noticed that it was becoming gradually weaker When Cadiot saw the horse it was greatly emaciated and feeble, with edema in the dependent parts of the body On the left side of the throat, a goiter-like swelling could be felt On the right, there was only a slight enlargement of the thyroid gland Over the carotids and several of their branches, as well as over the gluteal femoral arteries, strong pulsations were noticed The pulse rate was 80 Powerful pulsation could be felt when a hand was placed over the heart Exophthalmia was not present The temperature was 38 4° The symptoms became worse until death occurred three days after admission to the hospital The autopsy showed that the heart was hypertrophied The arge arteries had an enormous caliber and thin walls The left thyroid lobe was highly ascular and enlarged to more than ten times its normal volume

Marek (1223) observed, in the case of a Gidran mare which for six weeks would not lie down, a swelling of the thyroid gland, markedly protruding eyes, inability to close the eyelids, and a powerful cardiac palpitation The animal trembled when driven The sensitivity of the corneas and the whole skin was reduced, especially on the left side of the throat and in the sacral region Sight was almost gone (from what cause?)

Ries (1907) reported the case of a 12 year old mare which had a "powerful pulse", goiter, exophthalmia and excessive emaciation Extirpation of half the goiter resulted in considerable improvement

Among cattle, 4 cases of Basedow's disease have been described.

Roeder (1002) observed a well-nourished cow with protrusion of both eyes. The eyes were turned somewhat inward, so that the axis seemed to converge in the region of the end of the snout The lids gaped widely, and could scarcely be closed. The pulse rate was 90 to 100 beats per minute Even after very slight stimulation the easily excitable animal showed powerful cardiac palpitation. Dilatation of the heart could not be demonstrated The fist-sized goiter was rather hard A swelling of the thyroid gland was said to have been evident for four years

Gorig (1725) observed a ten year old cow with an egg-sized goiter and exophthalmia so great that the eyelids could not be closed The convergence of the eyes was noticed The autopsy showed hypertropy and dilatation of the left ventricule Gorig did not doubt that, during its lifetime, it had suffered from heart disorders. The examination evidently had not been very thorough

Kettritz (2691) described 2 cases of Basedow's disease in cattle. Both showed *goiter, cardiac dilatation, exophthalmos, and "strabismus convergens"*

In all cases where the eyes of the cattle showed a converging position, it was probably due to the anatomical peculiarities of these animals.

As may be gathered from this survey the picture of Basedow's disease in our domestic animals conforms in all essentials to that in man. Besides the chief signs a series of secondary signs is found The exophthalmia was absent in the case of one horse (Cadot). In all the other cases, the protrusion of the eyes was great, and in 6 of these the inability to close the eyelids was emphasized Probably this was due to the marked retraction of the upper lid Albrecht mentions it specifically Furthermore, the lack of associative movement of the upper eyelid during downward movement of the eyes is indicated One case progressed to abscess formation on the cornea (the female dog observed by Jewsejenko)

The animals were usually anemic and usually in a poor state of nutrition Only the cow observed by Roder was stated to be well nourished. Usually appetite was reduced A few times diarrhea and vomiting are mentioned

In several instances tachypnoea was mentioned, and once, in the case of a dog observed by Lellmann, there was also a nervous cough.

The animals were especially irritable and restless

In three cases a rise in temperature was noted; once (in a horse) up to 41° In a dog (Lellmann) the temperature was found to be normal In the other cases nothing is mentioned concerning temperature

In the case of one dog an urticaria-like skin eruption was observed and in another a lack of gloss of the hair.

Sainton (2877) expressed *the opinion that both of Jewsejenko's cases were to be* considered as examples of an infectious thyroiditis I cannot agree with him at all

The rise in temperature in such severe cases of Basedow's disease as those under discussion is *not* at all unusual (see §225 above) All the essential signs were plainly developed The case observed in the mare was a plain example of the acute form of Basedow's disease

In Cadot's case, also doubted by Sainton, the diagnosis of Basedow's disease is, in my opinion, certain notwithstanding the absence of exophthalmos

Görig's case should be omitted, since nothing except exophthalmos was present The small tumor on the thyroid gland seemed to Sainton to be connected with the protrusion of the eyes It must be admitted, however, that the examination during life was insufficient Nothing was said about the nature of the goiter, nor about a possible tachycardia But, leaving out of consideration the fact that no other cause was found for the bilateral exophthalmos, the smallness of the thyroid swelling is not evidence against its nature as a Basedow's disease goiter, and the changes in the heart, as shown by the autopsy, probably indicate intensified heart action during life

In the case of the female dog, observed by Jewsejenko, spontaneous improvement occurred, and, after a severe relapse, a cure In the case of the mare, rapid improvement followed thyroid gland extirpation Three dogs were put to death after treatment proved unsuccessful Two horses and a cow succumbed in a short time Nothing is known about the outcome in the rest of the cases.

The conspicuous preponderance of the female sex in animals with Basedow's disease is also apparent Sex is mentioned only in 9 out of 14 cases Seven were females: 2 dogs, 3 horses, 2 heads of cattle Two dogs were male.

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